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(54) Title: SCHIZOCHYTRIUM PKS GENES (57) Abstract The present invention relates to compositions and methods for preparing poly-unsaturated long chain fatty acids in plants, plant parts and plant cells, such as leaves, roots, fruits and seeds. Nucleic acid sequences and constructs encoding PKS-like genes required for the poly-unsaturated long chain fatty acid production, including the genes responsible for eicosapentenoic acid production of <i>Shewanella putrefaciens</i> and novel genes associated with the production of docosahexenoic acid in <i>Vibrio marinus</i> are used to generate transgenic plants, plant parts and cells which contain and express one or more transgenes encoding one or more of the PKS-like genes associated with such long chain poly-unsaturated fatty acid production. Expression of the PKS-like genes in the plant system permits the large scale production of poly-unsaturated long chain fatty acids such as eicosapentenoic acid and docosahexenoic acid for modification of the fatty acid profile of plants, plant parts and tissues. Manipulation of the fatty acid profiles allows for the production of commercial quantities of novel plant oils and products.		

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SCHIZOCHYTRIUM PKS GENES

5

INTRODUCTION

10 Field of the Invention

This invention relates to modulating levels of enzymes and/or enzyme components capable of modifying long chain poly-unsaturated fatty acids (PUFAs) in a host cell, and constructs and methods for producing PUFAs in a host cell. The invention is exemplified by production of eicosapentenoic acid (EPA) using genes derived from *Shewanella putrefaciens* and *Vibrio marinus*.

Background

Two main families of poly-unsaturated fatty acids (PUFAs) are the ω 3 fatty acids, exemplified by eicosapentenoic acid, and the ω 6 fatty acids, exemplified by arachidonic acid. PUFAs are important components of the plasma membrane of the cell, where they can be found in such forms as phospholipids, and also can be found in triglycerides. PUFAs also serve as precursors to other molecules of importance in human beings and animals, including the prostacyclins, leukotrienes and prostaglandins. Long chain PUFAs of importance include docosahexenoic acid (DHA) and eicosapentenoic acid (EPA), which are found primarily in different types of fish oil, gamma-linolenic acid (GLA), which is found in the seeds of a number of plants, including evening primrose (*Oenothera biennis*), borage (*Borago officinalis*) and black currants (*Ribes nigrum*), stearidonic acid (SDA), which is found in marine oils and plant seeds, and arachidonic acid (ARA), which along with GLA is found in filamentous fungi. ARA can be purified from animal tissues including liver and adrenal gland. Several genera of marine bacteria are known which synthesize either EPA or DHA. DHA is present in human milk along with ARA.

PUFAs are necessary for proper development, particularly in the developing infant brain, and for tissue formation and repair. As an example, DHA, is an important constituent of many human cell membranes, in particular nervous cells (gray matter), muscle cells, and spermatozoa and believed to affect the development of brain functions in general and to be essential for the development of eyesight. EPA and DHA have a number of nutritional and pharmacological uses. As an example adults affected by diabetes (especially non insulin-dependent) show

deficiencies and imbalances in their levels of DHA which are believed to contribute to later coronary conditions. Therefore a diet balanced in DHA may be beneficial to diabetics.

For DHA, a number of sources exist for commercial production including a variety of marine organisms, oils obtained from cold water marine fish, and egg yolk fractions. The purification of DHA from fish sources is relatively expensive due to technical difficulties, making DHA expensive and in short supply. In algae such as *Amphidinium* and *Schizochytrium* and marine fungi such as *Thraustochytrium* DHA may represent up to 48% of the fatty acid content of the cell. A few bacteria also are reported to produce DHA. These are generally deep sea bacteria such as *Vibrio marinus*. For ARA, microorganisms including the genera *Mortierella*, *Entomophthora*, *Phytium* and *Porphyridium* can be used for commercial production. Commercial sources of SDA include the genera *Trichodesma* and *Echium*. Commercial sources of GLA include evening primrose, black currants and borage. However, there are several disadvantages associated with commercial production of PUFAs from natural sources. Natural sources of PUFA, such as animals and plants, tend to have highly heterogeneous oil compositions. The oils obtained from these sources can require extensive purification to separate out one or more desired PUFA or to produce an oil which is enriched in one or more desired PUFA.

Natural sources also are subject to uncontrollable fluctuations in availability. Fish stocks may undergo natural variation or may be depleted by overfishing. Animal oils, and particularly fish oils, can accumulate environmental pollutants. Weather and disease can cause fluctuation in yields from both fish and plant sources. Cropland available for production of alternate oil-producing crops is subject to competition from the steady expansion of human populations and the associated increased need for food production on the remaining arable land. Crops which do produce PUFAs, such as borage, have not been adapted to commercial growth and may not perform well in monoculture. Growth of such crops is thus not economically competitive where more profitable and better established crops can be grown. Large-scale fermentation of organisms such as *Shewanella* also is expensive. Natural animal tissues contain low amounts of ARA and are difficult to process. Microorganisms such as *Porphyridium* and *Shewanella* are difficult to cultivate on a commercial scale.

Dietary supplements and pharmaceutical formulations containing PUFAs can retain the disadvantages of the PUFA source. Supplements such as fish oil capsules can contain low levels of the particular desired component and thus require large dosages. High dosages result in ingestion of high levels of undesired components, including contaminants. Care must be taken in providing fatty acid supplements, as overaddition may result in suppression of endogenous biosynthetic pathways and lead to competition with other necessary fatty acids in various lipid fractions *in vivo*, leading to undesirable results. For example, Eskimos having a diet high in ω 3 fatty acids have an increased tendency to bleed (U.S. Pat. No. 4,874,603). Fish oils have

unpleasant tastes and odors, which may be impossible to economically separate from the desired product, such as a food supplements. Unpleasant tastes and odors of the supplements can make such regimens involving the supplement undesirable and may inhibit compliance by the patient.

A number of enzymes have been identified as being involved in PUFA biosynthesis. Linoleic acid (LA, 18:2 Δ 9, 12) is produced from oleic acid (18:1 Δ 9) by a Δ 12-desaturase. GLA (18:3 Δ 6, 9, 12) is produced from linoleic acid (LA, 18:2 Δ 9, 12) by a Δ 6-desaturase. ARA (20:4 Δ 5, 8, 11, 14) is produced from DGLA (20:3 Δ 8, 11, 14), catalyzed by a Δ 5-desaturase. Eicosapentenoic acid (EPA) is a 20 carbon, omega 3 fatty acid containing 5 double bonds (Δ 5, 8, 11, 14, 17), all in the *cis* configuration. EPA, and the related DHA (Δ 4, 7, 10, 13, 16, 19, C22:6) are produced from oleic acid by a series of elongation and desaturation reactions. Additionally, an elongase (or elongases) is required to extend the 18 carbon PUFAs out to 20 and 22 carbon chain lengths. However, animals cannot convert oleic acid (18:1 Δ 9) into linoleic acid (18:2 Δ 9, 12). Likewise, μ -linolenic acid (ALA, 18:3 Δ 9, 12, 15) cannot be synthesized by mammals. Other eukaryotes, including fungi and plants, have enzymes which desaturate at positions Δ 12 and Δ 15. The major poly-unsaturated fatty acids of animals therefore are either derived from diet and/or from desaturation and elongation of linoleic acid (18:2 Δ 9, 12) or μ -linolenic acid (18:3 Δ 9, 12, 15).

Poly-unsaturated fatty acids are considered to be useful for nutritional, pharmaceutical, industrial, and other purposes. An expansive supply of poly-unsaturated fatty acids from natural sources and from chemical synthesis are not sufficient for commercial needs. Because a number of separate desaturase and elongase enzymes are required for fatty acid synthesis from linoleic acid (LA, 18:2 Δ 9, 12), common in most plant species, to the more saturated and longer chain PUFAs, engineering plant host cells for the expression of EPA and DHA may require expression of five or six separate enzyme activities to achieve expression, at least for EPA and DHA, and for production of quantities of such PUFAs additional engineering efforts may be required, for instance the down regulation of enzymes competing for substrate, engineering of higher enzyme activities such as by mutagenesis or targeting of enzymes to plastid organelles. Therefore it is of interest to obtain genetic material involved in PUFA biosynthesis from species that naturally produce these fatty acids and to express the isolated material alone or in combination in a heterologous system which can be manipulated to allow production of commercial quantities of PUFAs.

Relevant Literature

Several genera of marine bacteria have been identified which synthesize either EPA or DHA (DeLong and Yayanos, *Applied and Environmental Microbiology* (1986) 51: 730-737). Researchers of the Sagami Chemical Research Institute have reported EPA production in *E. coli* which have been transformed with a gene cluster from the marine bacterium, *Shewanella*

putrefaciens. A minimum of 5 open reading frames (ORFs) are required for fatty acid synthesis of EPA in *E. coli*. To date, extensive characterization of the functions of the proteins encoded by these genes has not been reported (Yazawa (1996) *Lipids* 31, S-297; WO 93/23545; WO 96/21735).

5 The protein sequence of open reading frame (ORF) 3 as published by Yazawa, USPN 5,683,898 is not a functional protein. Yazawa defines the protein as initiating at the methionine codon at nucleotides 9016-9014 of the *Shewanella* PKS-like cluster (Genbank accession U73935) and ending at the stop codon at nucleotides 8185-8183 of the *Shewanella* PKS-like cluster. However, when this ORF is expressed under control of a heterologous promoter in an *E.*
10 *coli* strain containing the entire PKS-like cluster except ORF 3, the recombinant cells do not produce EPA.

Polyketides are secondary metabolites the synthesis of which involves a set of enzymatic reactions analogous to those of fatty acid synthesis (see reviews: Hopwood and Sherman, *Annu. Rev. Genet.* (1990) 24: 37-66, and Katz and Donadio, in *Annual Review of Microbiology* (1993)
15 47: 875-912). It has been proposed to use polyketide synthases to produce novel antibiotics (Hutchinson and Fujii, *Annual Review of Microbiology* (1995) 49:201-238).

SUMMARY OF THE INVENTION

Novel compositions and methods are provided for preparation of long chain poly-
20 unsaturated fatty acids (PUFAs) using polyketide-like synthesis (PKS-like) genes in plants and plant cells. In contrast to the known and proposed methods for production of PUFAs by means of fatty acid synthesis genes, by the invention constructs and methods are provided for producing PUFAs by utilizing genes of a PKS-like system. The methods involve growing a host cell of interest transformed with an expression cassette functional in the host cell, the expression
25 cassette comprising a transcriptional and translational initiation regulatory region, joined in reading frame 5' to a DNA sequence to a gene or component of a PKS-like system capable of modulating the production of PUFAs (PKS-like gene). An alteration in the PUFA profile of host cells is achieved by expression following introduction of a complete PKS-like system responsible for a PUFA biosynthesis into host cells. The invention finds use for example in the
30 large scale production of DHA and EPA and for modification of the fatty acid profile of host cells and edible plant tissues and/or plant parts.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides designations for the ORFs of the EPA gene cluster of *Shewanella*.
35 Figure 1A shows the organization of the genes; those ORFs essential for EPA production in *E. coli* are numbered. Figure 1B shows the designations given to subclones.

Figure 2 provides the *Shewanella* PKS-like domain structure, motifs and 'Blast' matches of ORF 6 (Figure 2A), ORF 7 (Figure 2B), ORF 8 (Figure 2C), ORF 9 (Figure 2D) and ORF 3 (Figure 2E). Figure 2F shows the structure of the region of the Anabeana chromosome that is related to domains present in *Shewanella* EPA ORFs.

5 Figure 3 shows results for pantethenylation - ORF 3 in *E. coli* strain SJ16. The image shows [C^{14}] β -Alanine labelled proteins from *E. coli* (strain SJ16) cells transformed with the listed plasmids. Lane 1 represents pUC19, lane 2 represents pPA-NEB (Δ ORF 3), lane 3 represents pAA-Neb (EPA+), lane 4 represents ORF 6 subclone, lane 5 represents ORF 6 + ORF 3 subclones, and lane 6 represents ORF 3 subclone. ACP and an unknown (but previously
10 observed) 35 kD protein were labelled in all of the samples. The high molecular mass proteins detected in lanes 2 and 5 are full-length (largest band) and truncated products of the *Shewanella* ORF-6 gene (confirmed by Western analysis). *E. Coli* strain SJ16 is conditionally blocked in β -alanine synthesis.

Figure 4A shows the DNA sequence (SEQ ID NO:1) for the PKS-like cluster found in
15 *Shewanella*, containing ORF's 3-9. Figure 4B shows the amino acid sequence (SEQ ID NO:2) of ORF 2, which is coded by nucleotides 6121-8103 of the sequence shown in Fig 4A. Figure 4C shows the amino acid sequence (SEQ ID NO:3) of the published, inactive ORF3, translated from the strand complementary to that shown in Figure 4A, nucleotides 9016-8186. Figure 4D shows the nucleotide sequence 8186-9157 (SEQ ID NO:4); its complementary strand codes for
20 ORF 3 active in EPA synthesis. Figures 4E-J show the amino acid sequences (SEQ ID NOS:5-10) corresponding to ORF's 4-9, which are encoded by nucleotides 9681-12590 (SEQ ID NO:81), 13040-13903 (SEQ ID NO:82), 13906-22173 (SEQ ID NO:83), 22203-24515 (SEQ ID NO:84), 24518-30529 (SEQ ID NO:85) and 30730-32358 (SEQ ID NO:86), respectively, of Figure 4A. Figure 4K shows the amino acid sequence (SEQ ID NO:11) corresponding to
25 nucleotides 32834-34327.

Figure 5 shows the sequence (SEQ ID NO:12) for the PKS-like cluster in an approximately 40 kb DNA fragment of *Vibrio marinus*, containing ORFs 6, 7, 8 and 9. The start and last codons for each ORF are as follows: ORF 6: 17394, 25352; ORF 7: 25509, 28160; ORF 8: 28209, 34265; ORF 9: 34454, 36118.

30 Figure 6 shows the sequence (SEQ ID NO:13) for an approximately 19 kb portion of the PKS-like cluster of Figure 5 which contains the ORFs 6, 7, 8 and 9. The start and last codons for each ORF are as follows: ORF 6: 411, 8369 (SEQ ID NO:77); ORF 7: 8526, 11177 (SEQ ID NO:78); ORF 8: 11226, 17282 (SEQ ID NO:79); ORF 9: 17471, 19135 (SEQ ID NO:80).

35 Figure 7 shows a comparison of the PKS-like gene clusters of *Shewanella putrefaciens* and *Vibrio marinus*; Figure 7B is the *Vibrio marinus* operon sequence.

Figure 8 is an expanded view of the PKS-like gene cluster portion of *Vibrio marinus* shown in Figure 7B showing that ORFs 6, 7 and 8 are in reading frame 2, while ORF 9 is in reading frame 3.

Figure 9 demonstrates sequence homology of ORF 6 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 6 is depicted on the vertical axis, and the *Vibrio* ORF 6 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity. The repeated lines in the middle correspond to the multiple ACP domains found in ORF 6.

Figure 10 demonstrates sequence homology of ORF 7 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 7 is depicted on the vertical axis, and the *Vibrio* ORF 7 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 11 demonstrates sequence homology of ORF 8 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 8 is depicted on the vertical axis, and the *Vibrio* ORF 8 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 12 demonstrates sequence homology of ORF 9 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 9 is depicted on the vertical axis, and the *Vibrio* ORF 9 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 13 is a depiction of various complementation experiments, and resulting PUFA production. On the right, is shown the longest PUFA made in the *E. coli* strain containing the *Vibrio* and *Shewanella* genes depicted on the left. The hollow boxes indicate ORFs from *Shewanella*. The solid boxes indicate ORFs from *Vibrio*.

Figure 14 is a chromatogram showing fatty acid production from complementation of pEPAD8 from *Shewanella* (deletion ORF 8) with ORF 8 from *Shewanella*, in *E. coli* Fad E-. The chromatogram presents an EPA (20:5) peak.

Figure 15 is a chromatogram showing fatty acid production from complementation of pEPAD8 from *Shewanella* (deletion ORF 8) with ORF 8 from *Vibrio marinus*, in *E. coli* Fad E-. The chromatograph presents EPA (20:5) and DHA (22:6) peaks.

Figure 16 is a table of PUFA values from the ORF 8 complementation experiment, the chromatogram of which is shown in Figure 15.

Figure 17 is a plasmid map showing the elements of pCGN7770.

Figure 18 is a plasmid map showing the elements of pCGN8535.

Figure 19 is a plasmid map showing the elements of pCGN8537.

Figure 20 is a plasmid map showing the elements of pCGN8525.

Figure 21 is a comparison of the *Shewanella* ORFs as defined by Yazawa (1996) supra, and those disclosed in Figure 4. When a protein starting at the leucine (TTG) codon at nucleotides 9157-9155 and ending at the stop codon at nucleotides 8185-8183 is expressed under control of a heterologous promoter in an *E. coli* strain containing the entire PKS-like

cluster except ORF 3, the recombinant cells do produce EPA. Thus, the published protein sequence is likely to be wrong, and the coding sequence for the protein may start at the TTG codon at nucleotides 9157-9155 or the TTG codon at nucleotides 9172-9170. This information is critical to the expression of a functional PKS-like cluster heterologous system.

5 Figure 22 is a plasmid map showing the elements of pCGN8560.

Figure 23 is plasmid map showing the elements of pCGN8556.

Figure 24 shows the translated DNA sequence (SEQ ID NO:14) upstream of the published ORF 3 and the corresponding amino acids for which they code (SEQ ID NO:15). The ATG start codon at position 9016 is the start codon for the protein described by Yazawa *et al*
10 (1996) *supra*. The other arrows depict TTG or ATT codons that can also serve as start codons in bacteria. When ORF 3 is started from the published ATG codon at 9016, the protein is not functional in making EPA. When ORF 3 is initiated at the TTG codon at position 9157, the protein is capable of facilitating EPA synthesis.

Figure 25 shows the PCR product (SEQ ID NO:16) for SS9 Photobacter using primers in
15 Example 1.

Figure 26 shows probe sequences (SEQ ID NOS:17-31) resulting from PCR with primers presented in Example 1.

Figure 27 shows the nucleotide sequence of *Schizochytrium* EST clones A. LIB 3033-047-B5, LIB3033-046-E6 and a bridging PCR product have now been assembled into a partial
20 cDNA sequence (ORF6 homolog), B. LIB3033-046-D2 (hglc/ORF7/ORF8/ORF9 homolog), C. LIB81-015-D5, LIB81-042-B9 and a bridging PCR product have now been assembled into a partial cDNA sequence (ORF8/ORF9 homolog).

Figure 28 shows a schematic of the similarities between *Shewanella* PKS sequences and *Schizochytrium* sequences.

25 Figure 29 shows the amino acid sequences inferred from *Schizochytrium* EST clones A. ORF6 homolog, B. hglc/ORF7/ORF8/ORF9 homolog, C. ORF8/ORF9 homolog.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the subject invention, novel DNA sequences, DNA constructs and
30 methods are provided, which include some or all of the polyketide-like synthesis (PKS-like) pathway genes from *Shewanella*, *Vibrio*, *Schizochytrium* or other microorganisms, for modifying the poly-unsaturated long chain fatty acid content of host cells, particularly host plant cells. The present invention demonstrates that EPA synthesis genes in *Shewanella putrefaciens* constitute a polyketide-like synthesis pathway. Functions are ascribed to the *Shewanella*,
35 *Schizochytrium* and *Vibrio* genes and methods are provided for the production of EPA and DHA in host cells. The method includes the step of transforming cells with an expression cassette comprising a DNA encoding a polypeptide capable of increasing the amount of one or more

PUFA in the host cell. Desirably, integration constructs are prepared which provide for integration of the expression cassette into the genome of a host cell. Host cells are manipulated to express a sense or antisense DNA encoding a polypeptide(s) that has PKS-like gene activity. By "PKS-like gene" is intended a polypeptide which is responsible for any one or more of the functions of a PKS-like activity of interest. By "polypeptide" is meant any chain of amino acids, regardless of length or post-translational modification, for example, glycosylation or phosphorylation. Depending upon the nature of the host cell, the substrate(s) for the expressed enzyme may be produced by the host cell or may be exogenously supplied. Of particular interest is the selective control of PUFA production in plant tissues and/or plant parts such as leaves, roots, fruits and seeds. The invention can be used to synthesize EPA, DHA, and other related PUFAs in host cells.

There are many advantages to transgenic production of PUFAs. As an example, in transgenic *E. coli* as in *Shewanella*, EPA accumulates in the phospholipid fraction, specifically in the *sn*-2 position. It may be possible to produce a structured lipid in a desired host cell which differs substantially from that produced in either *Shewanella* or *E. coli*. Additionally transgenic production of PUFAs in particular host cells offers several advantages over purification from natural sources such as fish or plants. In transgenic plants, by utilizing a PKS-like system, fatty acid synthesis of PUFAs is achieved in the cytoplasm by a system which produces the PUFAs through *de novo* production of the fatty acids utilizing malonyl Co-A and acetyl Co-A as substrates. In this fashion, potential problems, such as those associated with substrate competition and diversion of normal products of fatty acid synthesis in a host to PUFA production, are avoided.

Production of fatty acids from recombinant plants provides the ability to alter the naturally occurring plant fatty acid profile by providing new synthetic pathways in the host or by suppressing undesired pathways, thereby increasing levels of desired PUFAs, or conjugated forms thereof, and decreasing levels of undesired PUFAs. Production of fatty acids in transgenic plants also offers the advantage that expression of PKS-like genes in particular tissues and/or plant parts means that greatly increased levels of desired PUFAs in those tissues and/or parts can be achieved, making recovery from those tissues more economical. Expression in a plant tissue and/or plant part presents certain efficiencies, particularly where the tissue or part is one which is easily harvested, such as seed, leaves, fruits, flowers, roots, etc. For example, the desired PUFAs can be expressed in seed; methods of isolating seed oils are well established. In addition to providing a source for purification of desired PUFAs, seed oil components can be manipulated through expression of PKS-like genes, either alone or in combination with other genes such as elongases, to provide seed oils having a particular PUFA profile in concentrated form. The concentrated seed oils then can be added to animal milks and/or synthetic or

semisynthetic milks to serve as infant formulas where human nursing is impossible or undesired, or in cases of malnourishment or disease in both adults and infants.

Transgenic microbial production of fatty acids offers the advantages that many microbes are known with greatly simplified oil compositions as compared with those of higher organisms, making purification of desired components easier. Microbial production is not subject to fluctuations caused by external variables such as weather and food supply. Microbially produced oil is substantially free of contamination by environmental pollutants. Additionally, microbes can provide PUFAs in particular forms which may have specific uses. For example, *Spirulina* can provide PUFAs predominantly at the first and third positions of triglycerides; digestion by pancreatic lipases preferentially releases fatty acids from these positions. Following human or animal ingestion of triglycerides derived from *Spirulina*, these PUFAs are released by pancreatic lipases as free fatty acids and thus are directly available, for example, for infant brain development. Additionally, microbial oil production can be manipulated by controlling culture conditions, notably by providing particular substrates for microbially expressed enzymes, or by addition of compounds which suppress undesired biochemical pathways. In addition to these advantages, production of fatty acids from recombinant microbes provides the ability to alter the naturally occurring microbial fatty acid profile by providing new synthetic pathways in the host or by suppressing undesired pathways, thereby increasing levels of desired PUFAs, or conjugated forms thereof, and decreasing levels of undesired PUFAs.

Production of fatty acids in animals also presents several advantages. Expression of desaturase genes in animals can produce greatly increased levels of desired PUFAs in animal tissues, making recovery from those tissues more economical. For example, where the desired PUFAs are expressed in the breast milk of animals, methods of isolating PUFAs from animal milk are well established. In addition to providing a source for purification of desired PUFAs, animal breast milk can be manipulated through expression of desaturase genes, either alone or in combination with other human genes, to provide animal milks with a PUFA composition substantially similar to human breast milk during the different stages of infant development. Humanized animal milks could serve as infant formulas where human nursing is impossible or undesired, or in the cases of malnourishment or disease.

DNAs encoding desired PKS-like genes can be identified in a variety of ways. In one method, a source of a desired PKS-like gene, for example genomic libraries from a *Shewanella*, *Schizochytrium* or *Vibrio* spp., is screened with detectable enzymatically- or chemically-synthesized probes. Sources of ORFs having PKS-like genes are those organisms which produce a desired PUFA, including DHA-producing or EPA-producing deep sea bacteria growing preferentially under high pressure or at relatively low temperature. Microorganisms such as *Shewanella* which produce EPA or DHA also can be used as a source of PKS-like genes. The probes can be made from DNA, RNA, or non-naturally occurring nucleotides, or mixtures

thereof. Probes can be enzymatically synthesized from DNAs of known PKS-like genes for normal or reduced-stringency hybridization methods. For discussions of nucleic acid probe design and annealing conditions, see, for example, Sambrook *et al*, *Molecular Cloning: A Laboratory Manual* (2nd ed.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989) or *Current*
5 *Protocols in Molecular Biology*, F. Ausubel *et al*, ed., Greene Publishing and Wiley-Interscience, New York (1987), each of which is incorporated herein by reference. Techniques for manipulation of nucleic acids encoding PUFA enzymes such as subcloning nucleic acid sequences encoding polypeptides into expression vectors, labelling probes, DNA hybridization, and the like are described generally in Sambrook, *supra*.

10 Oligonucleotide probes also can be used to screen sources and can be based on sequences of known PKS-like genes, including sequences conserved among known PKS-like genes, or on peptide sequences obtained from a desired purified protein. Oligonucleotide probes based on amino acid sequences can be degenerate to encompass the degeneracy of the genetic code, or can be biased in favor of the preferred codons of the source organism. Alternatively, a desired
15 protein can be entirely sequenced and total synthesis of a DNA encoding that polypeptide performed.

Once the desired DNA has been isolated, it can be sequenced by known methods. It is recognized in the art that such methods are subject to errors, such that multiple sequencing of the same region is routine and is still expected to lead to measurable rates of mistakes in the
20 resulting deduced sequence, particularly in regions having repeated domains, extensive secondary structure, or unusual base compositions, such as regions with high GC base content. When discrepancies arise, resequencing can be done and can employ special methods. Special methods can include altering sequencing conditions by using: different temperatures; different
25 enzymes; proteins which alter the ability of oligonucleotides to form higher order structures; altered nucleotides such as ITP or methylated dGTP; different gel compositions, for example adding formamide; different primers or primers located at different distances from the problem region; or different templates such as single stranded DNAs. Sequencing of mRNA can also be employed.

For the most part, some or all of the coding sequences for the polypeptides having PKS-
30 like gene activity are from a natural source. In some situations, however, it is desirable to modify all or a portion of the codons, for example, to enhance expression, by employing host preferred codons. Host preferred codons can be determined from the codons of highest frequency in the proteins expressed in the largest amount in a particular host species of interest. Thus, the coding sequence for a polypeptide having PKS-like gene activity can be synthesized
35 in whole or in part. All or portions of the DNA also can be synthesized to remove any destabilizing sequences or regions of secondary structure which would be present in the transcribed mRNA. All or portions of the DNA also can be synthesized to alter the base

composition to one more preferable to the desired host cell. Methods for synthesizing sequences and bringing sequences together are well established in the literature. *In vitro* mutagenesis and selection, site-directed mutagenesis, or other means can be employed to obtain mutations of naturally occurring PKS-like genes to produce a polypeptide having PKS-like gene activity *in vivo* with more desirable physical and kinetic parameters for function in the host cell, such as a longer half-life or a higher rate of production of a desired polyunsaturated fatty acid.

Of particular interest are the *Shewanella putrefaciens* ORFs and the corresponding ORFs of *Vibrio marinus* and *Schizochytrium*. The *Shewanella putrefaciens* PKS-like genes can be expressed in transgenic plants to effect biosynthesis of EPA. Other DNAs which are substantially identical in sequence to the *Shewanella putrefaciens* PKS-like genes, or which encode polypeptides which are substantially similar to PKS-like genes of *Shewanella putrefaciens* can be used, such as those identified from *Vibrio marinus* or *Schizochytrium*. By substantially identical in sequence is intended an amino acid sequence or nucleic acid sequence exhibiting in order of increasing preference at least 60%, 80%, 90% or 95% homology to the DNA sequence of the *Shewanella putrefaciens* PKS-like genes or nucleic acid sequences encoding the amino acid sequences for such genes. For polypeptides, the length of comparison sequences generally is at least 16 amino acids, preferably at least 20 amino acids, and most preferably 35 amino acids. For nucleic acids, the length of comparison sequences generally is at least 50 nucleotides, preferably at least 60 nucleotides, and more preferably at least 75 nucleotides, and most preferably, 110 nucleotides.

Homology typically is measured using sequence analysis software, for example, the Sequence Analysis software package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wisconsin 53705, MEGAlign (DNASar, Inc., 1228 S. Park St., Madison, Wisconsin 53715), and MacVector (Oxford Molecular Group, 2105 S. Bascom Avenue, Suite 200, Campbell, California 95008). BLAST (National Center for Biotechnology Information (NCBI) www.ncbi.nlm.gov; FASTA (Pearson and Lipman, *Science* (1985) 227:1435-1446). Such software matches similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine and leucine; aspartic acid, glutamic acid, asparagine, and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Substitutions may also be made on the basis of conserved hydrophobicity or hydrophilicity (Kyte and Doolittle, *J. Mol. Biol.* (1982) 157: 105-132), or on the basis of the ability to assume similar polypeptide secondary structure (Chou and Fasman, *Adv. Enzymol.* (1978) 47: 45-148, 1978). A related protein to the probing sequence is identified when $p \geq 0.01$, preferably $p \geq 10^{-7}$ or 10^{-8} .

Encompassed by the present invention are related PKS-like genes from the same or other organisms. Such related PKS-like genes include variants of the disclosed PKS-like ORFs that occur naturally within the same or different species of *Shewanella*, as well as homologues of the disclosed PKS-like genes from other species and evolutionarily related proteins having analogous function and activity. Also included are PKS-like genes which, although not substantially identical to the *Shewanella putrefaciens* PKS-like genes, operate in a similar fashion to produce PUFAs as part of a PKS-like system. Related PKS-like genes can be identified by their ability to function substantially the same as the disclosed PKS-like genes; that is, they can be substituted for corresponding ORFs of *Shewanella*, *Schizochytrium* or *Vibrio* and still effectively produce EPA or DHA. Related PKS-like genes also can be identified by screening sequence databases for sequences homologous to the disclosed PKS-like genes, by hybridization of a probe based on the disclosed PKS-like genes to a library constructed from the source organism, or by RT-PCR using mRNA from the source organism and primers based on the disclosed PKS-like gene. Thus, the phrase "PKS-like genes" refers not only to the nucleotide sequences disclosed herein, but also to other nucleic acids that are allelic or species variants of these nucleotide sequences. It is also understood that these terms include nonnatural mutations introduced by deliberate mutation using recombinant technology such as single site mutation or by excising short sections of DNA open reading frames coding for PUFA enzymes or by substituting new codons or adding new codons. Such minor alterations substantially maintain the immunoidentity of the original expression product and/or its biological activity. The biological properties of the altered PUFA enzymes can be determined by expressing the enzymes in an appropriate cell line and by determining the ability of the enzymes to synthesize PUFAs. Particular enzyme modifications considered minor would include substitution of amino acids of similar chemical properties, e.g., glutamic acid for aspartic acid or glutamine for asparagine.

When utilizing a PUFA PKS-like system from another organism, the regions of a PKS-like gene polypeptide important for PKS-like gene activity can be determined through routine mutagenesis, expression of the resulting mutant polypeptides and determination of their activities. The coding region for the mutants can include deletions, insertions and point mutations, or combinations thereof. A typical functional analysis begins with deletion mutagenesis to determine the N- and C-terminal limits of the protein necessary for function, and then internal deletions, insertions or point mutants are made in the open ready frame to further determine regions necessary for function. Other techniques such as cassette mutagenesis or total synthesis also can be used. Deletion mutagenesis is accomplished, for example, by using exonucleases to sequentially remove the 5' or 3' coding regions. Kits are available for such techniques. After deletion, the coding region is completed by ligating oligonucleotides containing start or stop codons to the deleted coding region after 5' or 3' deletion, respectively.

Alternatively, oligonucleotides encoding start or stop codons are inserted into the coding region by a variety of methods including site-directed mutagenesis, mutagenic PCR or by ligation onto DNA digested at existing restriction sites. Internal deletions can similarly be made through a variety of methods including the use of existing restriction sites in the DNA, by use of mutagenic primers via site directed mutagenesis or mutagenic PCR. Insertions are made through methods such as linker-scanning mutagenesis, site-directed mutagenesis or mutagenic PCR. Point mutations are made through techniques such as site-directed mutagenesis or mutagenic PCR.

Chemical mutagenesis also can be used for identifying regions of a PKS-like gene polypeptide important for activity. A mutated construct is expressed, and the ability of the resulting altered protein to function as a PKS-like gene is assayed. Such structure-function analysis can determine which regions may be deleted, which regions tolerate insertions, and which point mutations allow the mutant protein to function in substantially the same way as the native PKS-like gene. All such mutant proteins and nucleotide sequences encoding them are within the scope of the present invention. EPA is produced in *Shewanella* as the product of a PKS-like system, such that the EPA genes encode components of this system. In *Vibrio*, DHA is produced by a similar system. The enzymes which synthesize these fatty acids are encoded by a cluster of genes which are distinct from the fatty acid synthesis genes encoding the enzymes involved in synthesis of the C16 and C18 fatty acids typically found in bacteria and in plants. As the *Shewanella* EPA genes represent a PKS-like gene cluster, EPA production is, at least to some extent, independent of the typical bacterial type II FAS system. Thus, production of EPA in the cytoplasm of plant cells can be achieved by expression of the PKS-like pathway genes in plant cells under the control of appropriate plant regulatory signals.

EPA production in *E. coli* transformed with the *Shewanella* EPA genes proceeds during anaerobic growth, indicating that O₂-dependent desaturase reactions are not involved. Analyses of the proteins encoded by the ORFs essential for EPA production reveals the presence of domain structures characteristic of PKS-like systems. Fig. 2A shows a summary of the domains, motifs, and also key homologies detected by "BLAST" data bank searches. Because EPA is different from many of the other substances produced by PKS-like pathways, i.e., it contains 5, *cis* double bonds, spaced at 3 carbon intervals along the molecule, a PKS-like system for synthesis of EPA is not expected.

Further, BLAST searches using the domains present in the *Shewanella* EPA ORFs reveal that several are related to proteins encoded by a PKS-like gene cluster found in Anabaena. The structure of that region of the Anabaena chromosome is shown in Fig. 2F. The Anabaena PKS-like genes have been linked to the synthesis of a long-chain (C26), hydroxy-fatty acid found in a glycolipid layer of heterocysts. The EPA protein domains with homology to the Anabaena proteins are indicated in Fig. 2F.

ORF 6 of *Shewanella* contains a KAS domain which includes an active site motif (DXAC*), SEQ ID NO:32, as well as a "GFGG", SEQ ID NO:33, motif which is present at the end of many Type II KAS proteins (see Fig. 2A). Extended motifs are present but not shown here. Next is a malonyl-CoA:ACP acyl transferase (AT) domain. Sequences near the active site motif (GHS**XG*), SEQ ID NO:34, suggest it transfers malonate rather than methylmalonate, i.e., it resembles the acetate-like ATs. Following a linker region, there is a cluster of 6 repeating domains, each ~100 amino acids in length, which are homologous to PKS-like ACP sequences. Each contains a pantetheine binding site motif (LGXDS*(L/I)), SEQ ID NOS:35 and 36. The presence of 6 such ACP domains has not been observed previously in fatty acid synthases (FAS) or PKS-like systems. Near the end of the protein is a region which shows homology to β -keto-ACP reductases (KR). It contains a pyridine nucleotide binding site motif "GXGXX(G/A/P)", SEQ ID NOS:37, 38 and 39.

The *Shewanella* ORF 8 begins with a KAS domain, including active site and ending motifs (Fig. 2C). The best match in the data banks is with the Anabeana HglD. There is also a domain which has sequence homology to the N-terminal one half of the Anabeana HglC. This region also shows weak homology to KAS proteins although it lacks the active site and ending motifs. It has the characteristics of the so-called chain length factors (CLF) of Type II PKS-like systems. ORF 8 appears to direct the production of EPA versus DHA by the PKS-like system. ORF 8 also has two domains with homology to β -hydroxyacyl-ACP dehydrases (DH). The best match for both domains is with *E. coli* FabA, a bi-functional enzyme which carries out both the dehydrase reaction and an isomerization (*trans* to *cis*) of the resulting double bond. The first DH domain contains both the active site histidine (H) and an adjacent cysteine (C) implicated in FabA catalysis. The second DH domain has the active site H but lacks the adjacent C (Fig. 2C). Blast searches with the second DH domain also show matches to FabZ, a second *E. coli* DH, which does not possess isomerase activity.

The N-terminal half of ORF 7 (Fig. 2B) has no significant matches in the data banks. The best match of the C-terminal half is with a C-terminal portion of the Anabeana HglC. This domain contains an acyl-transferase (AT) motif (GX~~S~~XG), SEQ ID NO:40. Comparison of the extended active site sequences, based on the crystal structure of the *E. coli* malonyl-CoA:ACP AT, reveals that ORF 7 lacks two residues essential for exclusion of water from the active site (*E. coli* nomenclature; Q11 and R117). These data suggest that ORF 7 may function as a thioesterase.

ORF 9 (Fig. 2D) is homologous to an ORF of unknown function in the Anabeana Hgl cluster. It also exhibits a very weak homology to NIFA, a regulatory protein in nitrogen fixing bacteria. A regulatory role for the ORF 9 protein has not been excluded. ORF 3 (Fig. 2E) is homologous to the Anabeana HetI as well as EntD from *E. coli* and Sfp of *Bacillus*. Recently, a new enzyme family of phosphopantetheinyl transferases has been identified that includes HetI,

EntD and Sfp (Lamblot RH, *et al.* (1996) A new enzyme superfamily - the phosphopantetheinyl transferases. *Chemistry & Biology*, Vol 3, #11, 923-936). The data of Fig. 3 demonstrates that the presence of ORF 3 is required for addition of β -alanine (i.e. pantetheine) to the ORF 6 protein. Thus, ORF 3 encodes the phosphopantetheinyl transferase specific for the ORF 6 ACP domains. (See, Haydock SF *et al.* (1995) Divergent sequence motifs correlated with the substrate specificity of (methyl)malonyl-CoA:acyl carrier protein transacylase domains in modular polyketide synthases, *FEBS Lett.*, 374, 246-248). Malonate is the source of the carbons utilized in the extension reactions of EPA synthesis. Additionally, malonyl-CoA rather than malonyl-ACP is the AT substrate, i.e., the AT region of ORF 6 uses malonyl Co-A.

Once the DNA sequences encoding the PKS-like genes of an organism responsible for PUFA production have been obtained, they are placed in a vector capable of replication in a host cell, or propagated *in vitro* by means of techniques such as PCR or long PCR. Replicating vectors can include plasmids, phage, viruses, cosmids and the like. Desirable vectors include those useful for mutagenesis of the gene of interest or for expression of the gene of interest in host cells. A PUFA synthesis enzyme or a homologous protein can be expressed in a variety of recombinantly engineered cells. Numerous expression systems are available for expression of DNA encoding a PUFA enzyme. The expression of natural or synthetic nucleic acids encoding PUFA enzyme is typically achieved by operably linking the DNA to a promoter (which is either constitutive or inducible) within an expression vector. By expression vector is meant a DNA molecule, linear or circular, that comprises a segment encoding a PUFA enzyme, operably linked to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences. An expression vector also may include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors generally are derived from plasmid or viral DNA, and can contain elements of both. The term "operably linked" indicates that the segments are arranged so that they function in concert for their intended purposes, for example, transcription initiates in the promoter and proceeds through the coding segment to the terminator. See Sambrook *et al*, *supra*.

The technique of long PCR has made *in vitro* propagation of large constructs possible, so that modifications to the gene of interest, such as mutagenesis or addition of expression signals, and propagation of the resulting constructs can occur entirely *in vitro* without the use of a replicating vector or a host cell. *In vitro* expression can be accomplished, for example, by placing the coding region for the desaturase polypeptide in an expression vector designed for *in vitro* use and adding rabbit reticulocyte lysate and cofactors; labeled amino acids can be incorporated if desired. Such *in vitro* expression vectors may provide some or all of the expression signals necessary in the system used. These methods are well known in the art and the components of the system are commercially available. The reaction mixture can then be

assayed directly for PKS-like enzymes for example by determining their activity, or the synthesized enzyme can be purified and then assayed.

Expression in a host cell can be accomplished in a transient or stable fashion. Transient expression can occur from introduced constructs which contain expression signals functional in the host cell, but which constructs do not replicate and rarely integrate in the host cell, or where the host cell is not proliferating. Transient expression also can be accomplished by inducing the activity of a regulatable promoter operably linked to the gene of interest, although such inducible systems frequently exhibit a low basal level of expression. Stable expression can be achieved by introduction of a nucleic acid construct that can integrate into the host genome or that autonomously replicates in the host cell. Stable expression of the gene of interest can be selected for through the use of a selectable marker located on or transfected with the expression construct, followed by selection for cells expressing the marker. When stable expression results from integration, integration of constructs can occur randomly within the host genome or can be targeted through the use of constructs containing regions of homology with the host genome sufficient to target recombination with the host locus. Where constructs are targeted to an endogenous locus, all or some of the transcriptional and translational regulatory regions can be provided by the endogenous locus. To achieve expression in a host cell, the transformed DNA is operably associated with transcriptional and translational initiation and termination regulatory regions that are functional in the host cell.

Transcriptional and translational initiation and termination regions are derived from a variety of nonexclusive sources, including the DNA to be expressed, genes known or suspected to be capable of expression in the desired system, expression vectors, chemical synthesis. The termination region can be derived from the 3' region of the gene from which the initiation region was obtained or from a different gene. A large number of termination regions are known to and have been found to be satisfactory in a variety of hosts from the same and different genera and species. The termination region usually is selected more as a matter of convenience rather than because of any particular property. When expressing more than one PKS-like ORF in the same cell, appropriate regulatory regions and expression methods should be used. Introduced genes can be propagated in the host cell through use of replicating vectors or by integration into the host genome. Where two or more genes are expressed from separate replicating vectors, it is desirable that each vector has a different means of replication. Each introduced construct, whether integrated or not, should have a different means of selection and should lack homology to the other constructs to maintain stable expression and prevent reassortment of elements among constructs. Judicious choices of regulatory regions, selection means and method of propagation of the introduced construct can be experimentally determined so that all introduced genes are expressed at the necessary levels to provide for synthesis of the desired products.

A variety of procaryotic expression systems can be used to express PUFA enzyme. Expression vectors can be constructed which contain a promoter to direct transcription, a ribosome binding site, and a transcriptional terminator. Examples of regulatory regions suitable for this purpose in *E. coli* are the promoter and operator region of the *E. coli* tryptophan biosynthetic pathway as described by Yanofsky (1984) *J. Bacteriol.*, 158:1018-1024 and the leftward promoter of phage lambda ($P\lambda$) as described by Herskowitz and Hagen, (1980) *Ann. Rev. Genet.*, 14:399-445. The inclusion of selection markers in DNA vectors transformed in *E. coli* is also useful. Examples of such markers include genes specifying resistance to ampicillin, tetracycline, or chloramphenicol. Vectors used for expressing foreign genes in bacterial hosts generally will contain a selectable marker, such as a gene for antibiotic resistance, and a promoter which functions in the host cell. Plasmids useful for transforming bacteria include pBR322 (Bolivar, *et al.*, (1977) *Gene* 2:95-113), the pUC plasmids (Messing, (1983) *Meth. Enzymol.* 101:20-77, Vieira and Messing, (1982) *Gene* 19:259-268), pCQV2 (Queen, *ibid.*), and derivatives thereof. Plasmids may contain both viral and bacterial elements. Methods for the recovery of the proteins in biologically active form are discussed in U.S. Patent Nos. 4,966,963 and 4,999,422, which are incorporated herein by reference. See Sambrook, *et al* for a description of other prokaryotic expression systems.

For expression in eukaryotes, host cells for use in practicing the present invention include mammalian, avian, plant, insect, and fungal cells. As an example, for plants, the choice of a promoter will depend in part upon whether constitutive or inducible expression is desired and whether it is desirable to produce the PUFAs at a particular stage of plant development and/or in a particular tissue. Considerations for choosing a specific tissue and/or developmental stage for expression of the ORFs may depend on competing substrates or the ability of the host cell to tolerate expression of a particular PUFA. Expression can be targeted to a particular location within a host plant such as seed, leaves, fruits, flowers, and roots, by using specific regulatory sequences, such as those described in USPN 5,463,174, USPN 4,943,674, USPN 5,106,739, USPN 5,175,095, USPN 5,420,034, USPN 5,188,958, and USPN 5,589,379. Where the host cell is a yeast, transcription and translational regions functional in yeast cells are provided, particularly from the host species. The transcriptional initiation regulatory regions can be obtained, for example from genes in the glycolytic pathway, such as alcohol dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase (GPD), phosphoglucoisomerase, phosphoglycerate kinase, etc. or regulatable genes such as acid phosphatase, lactase, metallothionein, glucoamylase, etc. Any one of a number of regulatory sequences can be used in a particular situation, depending upon whether constitutive or induced transcription is desired, the particular efficiency of the promoter in conjunction with the open-reading frame of interest, the ability to join a strong promoter with a control region from a different promoter which allows for inducible transcription, ease of construction, and the like. Of particular interest are promoters

which are activated in the presence of galactose. Galactose-inducible promoters (GAL1, GAL7, and GAL10) have been extensively utilized for high level and regulated expression of protein in yeast (Lue *et al*, (1987) *Mol. Cell. Biol.* 7:3446; Johnston, (1987) *Microbiol. Rev.* 51:458).

Transcription from the GAL promoters is activated by the GAL4 protein, which binds to the promoter region and activates transcription when galactose is present. In the absence of galactose, the antagonist GAL80 binds to GAL4 and prevents GAL4 from activating transcription. Addition of galactose prevents GAL80 from inhibiting activation by GAL4.

Preferably, the termination region is derived from a yeast gene, particularly *Saccharomyces*, *Schizosaccharomyces*, *Candida* or *Kluyveromyces*. The 3' regions of two mammalian genes, γ interferon and $\alpha 2$ interferon, are also known to function in yeast.

Nucleotide sequences surrounding the translational initiation codon ATG have been found to affect expression in yeast cells. If the desired polypeptide is poorly expressed in yeast, the nucleotide sequences of exogenous genes can be modified to include an efficient yeast translation initiation sequence to obtain optimal gene expression. For expression in *Saccharomyces*, this can be done by site-directed mutagenesis of an inefficiently expressed gene by fusing it in-frame to an endogenous *Saccharomyces* gene, preferably a highly expressed gene, such as the lactase gene.

As an alternative to expressing the PKS-like genes in the plant cell cytoplasm, is to target the enzymes to the chloroplast. One method to target proteins to the chloroplast entails use of leader peptides attached to the N-termini of the proteins. Commonly used leader peptides are derived from the small subunit of plant ribulose bis phosphate carboxylase. Leader sequences from other chloroplast proteins may also be used. Another method for targeting proteins to the chloroplast is to transform the chloroplast genome (Stable transformation of chloroplasts of *Chlamydomonas reinhardtii* (1 green alga) using bombardment of recipient cells with high-velocity tungsten microprojectiles coated with foreign DNA has been described. See, for example, Blowers *et al Plant Cell* (1989) 1:123-132 and Debuchy *et al EMBO J* (1989) 8:2803-2809. The transformation technique, using tungsten microprojectiles, is described by Kline *et al, Nature* (London) (1987) 327:70-73). The most common method of transforming chloroplasts involves using biolistic techniques, but other techniques developed for the purpose may also be used. (Methods for targeting foreign gene products into chloroplasts (Shrier *et al EMBO J.* (1985) 4:25-32) or mitochondria (Boutry *et al, supra*) have been described. See also Tomai *et al Gen. Biol. Chem.* (1988) 263:15104-15109 and US Patent No. 4,940,835 for the use of transit peptides for translocating nuclear gene products into the chloroplast. Methods for directing the transport of proteins to the chloroplast are reviewed in Kenauf *TIBTECH* (1987) 5:40-47.

For producing PUFAs in avian species and cells, gene transfer can be performed by introducing a nucleic acid sequence encoding a PUFA enzyme into the cells following procedures known in the art. If a transgenic animal is desired, pluripotent stem cells of embryos

can be provided with a vector carrying a PUFA enzyme encoding transgene and developed into adult animal (USPN 5,162,215; Ono *et al.* (1996) *Comparative Biochemistry and Physiology A* 113(3):287-292; WO 9612793; WO 9606160). In most cases, the transgene is modified to express high levels of the PKS-like enzymes in order to increase production of PUFAs. The transgenes can be modified, for example, by providing transcriptional and/or translational regulatory regions that function in avian cells, such as promoters which direct expression in particular tissues and egg parts such as yolk. The gene regulatory regions can be obtained from a variety of sources, including chicken anemia or avian leukosis viruses or avian genes such as a chicken ovalbumin gene.

Production of PUFAs in insect cells can be conducted using baculovirus expression vectors harboring PKS-like transgenes. Baculovirus expression vectors are available from several commercial sources such as Clontech. Methods for producing hybrid and transgenic strains of algae, such as marine algae, which contain and express a desaturase transgene also are provided. For example, transgenic marine algae can be prepared as described in USPN 5,426,040. As with the other expression systems described above, the timing, extent of expression and activity of the desaturase transgene can be regulated by fitting the polypeptide coding sequence with the appropriate transcriptional and translational regulatory regions selected for a particular use. Of particular interest are promoter regions which can be induced under preselected growth conditions. For example, introduction of temperature sensitive and/or metabolite responsive mutations into the desaturase transgene coding sequences, its regulatory regions, and/or the genome of cells into which the transgene is introduced can be used for this purpose.

The transformed host cell is grown under appropriate conditions adapted for a desired end result. For host cells grown in culture, the conditions are typically optimized to produce the greatest or most economical yield of PUFAs, which relates to the selected desaturase activity. Media conditions which may be optimized include: carbon source, nitrogen source, addition of substrate, final concentration of added substrate, form of substrate added, aerobic or anaerobic growth, growth temperature, inducing agent, induction temperature, growth phase at induction, growth phase at harvest, pH, density, and maintenance of selection. Microorganisms such as yeast, for example, are preferably grown using selected media of interest, which include yeast peptone broth (YPD) and minimal media (contains amino acids, yeast nitrogen base, and ammonium sulfate, and lacks a component for selection, for example uracil). Desirably, substrates to be added are first dissolved in ethanol. Where necessary, expression of the polypeptide of interest may be induced, for example by including or adding galactose to induce expression from a GAL promoter.

When increased expression of the PKS-like gene polypeptide in a host cell which expresses PUFA from a PKS-like system is desired, several methods can be employed.

Additional genes encoding the PKS-like gene polypeptide can be introduced into the host organism. Expression from the native PKS-like gene locus also can be increased through homologous recombination, for example by inserting a stronger promoter into the host genome to cause increased expression, by removing destabilizing sequences from either the mRNA or the encoded protein by deleting that information from the host genome, or by adding stabilizing sequences to the mRNA (*see* USPN 4,910,141 and USPN 5,500,365). Thus, the subject host will have at least have one copy of the expression construct and may have two or more, depending upon whether the gene is integrated into the genome, amplified, or is present on an extrachromosomal element having multiple copy numbers. Where the subject host is a yeast, four principal types of yeast plasmid vectors can be used: Yeast Integrating plasmids (YIps), Yeast Replicating plasmids (YRps), Yeast Centromere plasmids (YCps), and Yeast Episomal plasmids (YEpS). YIps lack a yeast replication origin and must be propagated as integrated elements in the yeast genome. YRps have a chromosomally derived autonomously replicating sequence and are propagated as medium copy number (20 to 40), autonomously replicating, unstably segregating plasmids. YCps have both a replication origin and a centromere sequence and propagate as low copy number (10-20), autonomously replicating, stably segregating plasmids. YEpS have an origin of replication from the yeast 2 μ m plasmid and are propagated as high copy number, autonomously replicating, irregularly segregating plasmids. The presence of the plasmids in yeast can be ensured by maintaining selection for a marker on the plasmid. Of particular interest are the yeast vectors pYES2 (a YEp plasmid available from Invitrogen, confers uracil prototrophy and a GAL1 galactose-inducible promoter for expression), and pYX424 (a YEp plasmid having a constitutive TP1 promoter and conferring leucine prototrophy; (Alber and Kawasaki (1982). *J. Mol. & Appl. Genetics* 1: 419).

The choice of a host cell is influenced in part by the desired PUFA profile of the transgenic cell, and the native profile of the host cell. Even where the host cell expresses PKS-like gene activity for one PUFA, expression of PKS-like genes of another PKS-like system can provide for production of a novel PUFA not produced by the host cell. In particular instances where expression of PKS-like gene activity is coupled with expression of an ORF 8 PKS-like gene of an organism which produces a different PUFA, it can be desirable that the host cell naturally have, or be mutated to have, low PKS-like gene activity for ORF 8. As an example, for production of EPA, the DNA sequence used encodes the polypeptide having PKS-like gene activity of an organism which produces EPA, while for production of DHA, the DNA sequences used are those from an organism which produces DHA. For use in a host cell which already expresses PKS-like gene activity it can be necessary to utilize an expression cassette which provides for overexpression of the desired PKS-like genes alone or with a construct to downregulate the activity of an existing ORF of the existing PKS-like system, such as by antisense or co-suppression. Similarly, a combination of ORFs derived from separate organisms

which produce the same or different PUFAs using PKS-like systems may be used. For instance, the ORF 8 of *Vibrio* directs the expression of DHA in a host cell, even when ORFs 3, 6, 7 and 9 are from *Shewanella*, which produce EPA when coupled to ORF 8 of *Shewanella*. Therefore, for production of eicosapentanoic acid (EPA), the expression cassettes used generally include one or more cassettes which include ORFs 3, 6, 7, 8 and 9 from a PUFA-producing organism such as the marine bacterium *Shewanella putrefaciens* (for EPA production) or *Vibrio marinus* (for DHA production). ORF 8 can be used for induction of DHA production, and ORF 8 of *Vibrio* can be used in conjunction with ORFs 3, 6, 7 and 9 of *Shewanella* to produce DHA. The organization and numbering scheme of the ORFs identified in the *Shewanella* gene cluster are shown in Fig 1A. Maps of several subclones referred to in this study are shown in Fig 1B. For expression of a PKS-like gene polypeptide, transcriptional and translational initiation and termination regions functional in the host cell are operably linked to the DNA encoding the PKS-like gene polypeptide.

Constructs comprising the PKS-like ORFs of interest can be introduced into a host cell by any of a variety of standard techniques, depending in part upon the type of host cell. These techniques include transfection, infection, bolistic impact, electroporation, microinjection, scraping, or any other method which introduces the gene of interest into the host cell (*see* USPN 4,743,548, USPN 4,795,855, USPN 5,068,193, USPN 5,188,958, USPN 5,463,174, USPN 5,565,346 and USPN 5,565,347). Methods of transformation which are used include lithium acetate transformation (*Methods in Enzymology*, (1991) 194:186-187). For convenience, a host cell which has been manipulated by any method to take up a DNA sequence or construct will be referred to as "transformed" or "recombinant" herein. The subject host will have at least have one copy of the expression construct and may have two or more, depending upon whether the gene is integrated into the genome, amplified, or is present on an extrachromosomal element having multiple copy numbers.

For production of PUFAs, depending upon the host cell, the several polypeptides produced by pEPA, ORFs 3, 6, 7, 8 and 9, are introduced as individual expression constructs or can be combined into two or more cassettes which are introduced individually or co-transformed into a host cell. A standard transformation protocol is used. For plants, where less than all PKS-like genes required for PUFA synthesis have been inserted into a single plant, plants containing a complementing gene or genes can be crossed to obtain plants containing a full complement of PKS-like genes to synthesize a desired PUFA.

The PKS-like-mediated production of PUFAs can be performed in either prokaryotic or eukaryotic host cells. The cells can be cultured or formed as part or all of a host organism including an animal. Viruses and bacteriophage also can be used with appropriate cells in the production of PUFAs, particularly for gene transfer, cellular targeting and selection. Any type of plant cell can be used for host cells, including dicotyledonous plants, monocotyledonous plants,

and cereals. Of particular interest are crop plants such as *Brassica*, *Arabidopsis*, soybean, corn, and the like. Prokaryotic cells of interest include *Eschericia*, *Baccillus*, *Lactobaccillus*, *cyanobacteria* and the like. Eukaryotic cells include plant cells, mammalian cells such as those of lactating animals, avian cells such as of chickens, and other cells amenable to genetic manipulation including insect, fungal, and algae cells. Examples of host animals include mice, rats, rabbits, chickens, quail, turkeys, cattle, sheep, pigs, goats, yaks, etc., which are amenable to genetic manipulation and cloning for rapid expansion of a transgene expressing population. For animals, PKS-like transgenes can be adapted for expression in target organelles, tissues and body fluids through modification of the gene regulatory regions. Of particular interest is the production of PUFAs in the breast milk of the host animal.

Examples of host microorganisms include *Saccharomyces cerevisiae*, *Saccharomyces carlsbergensis*, or other yeast such as *Candida*, *Kluyveromyces* or other fungi, for example, filamentous fungi such as *Aspergillus*, *Neurospora*, *Penicillium*, etc. Desirable characteristics of a host microorganism are, for example, that it is genetically well characterized, can be used for high level expression of the product using ultra-high density fermentation, and is on the GRAS (generally recognized as safe) list since the proposed end product is intended for ingestion by humans. Of particular interest is use of a yeast, more particularly baker's yeast (*S. cerevisiae*), as a cell host in the subject invention. Strains of particular interest are SC334 (Mat α pep4-3 prbl-1122 ura3-52 leu2-3, 112 reg1-501 gal1; (Hovland *et al* (1989) Gene 83:57-64); BJ1995 (Yeast Genetic Stock Centre, 1021 Donner Laboratory, Berkeley, CA 94720), INVSC1 (Mat α hiw3 Δ 1 leu2 trp1-289 ura3-52 (Invitrogen, 1600 Faraday Ave., Carlsbad, CA 92008) and INVSC2 (Mat α his3 Δ 200 ura3-167; (Invitrogen). Bacterial cells also may be used as hosts. This includes *E. coli*, which can be useful in fermentation processes. Alternatively, a host such as a *Lactobacillus* species can be used as a host for introducing the products of the PKS-like pathway into a product such as yogurt.

The transformed host cell can be identified by selection for a marker contained on the introduced construct. Alternatively, a separate marker construct can be introduced with the desired construct, as many transformation techniques introduce multiple DNA molecules into host cells. Typically, transformed hosts are selected for their ability to grow on selective media. Selective media can incorporate an antibiotic or lack a factor necessary for growth of the untransformed host, such as a nutrient or growth factor. An introduced marker gene therefor may confer antibiotic resistance, or encode an essential growth factor or enzyme, and permit growth on selective media when expressed in the transformed host cell. Desirably, resistance to kanamycin and the amino glycoside G418 are of particular interest (*see* USPN 5,034,322). For yeast transformants, any marker that functions in yeast can be used, such as the ability to grow on media lacking uracil, lencine, lysine or tryptophan.

Selection of a transformed host also can occur when the expressed marker protein can be detected, either directly or indirectly. The marker protein can be expressed alone or as a fusion to another protein. The marker protein can be one which is detected by its enzymatic activity; for example β -galactosidase can convert the substrate X-gal to a colored product, and luciferase
5 can convert luciferin to a light-emitting product. The marker protein can be one which is detected by its light-producing or modifying characteristics; for example, the green fluorescent protein of *Aequorea victoria* fluoresces when illuminated with blue light. Antibodies can be used to detect the marker protein or a molecular tag on, for example, a protein of interest. Cells expressing the marker protein or tag can be selected, for example, visually, or by techniques
10 such as FACS or panning using antibodies.

The PUFAs produced using the subject methods and compositions are found in the host plant tissue and/or plant part as free fatty acids and/or in conjugated forms such as acylglycerols, phospholipids, sulfolipids or glycolipids, and can be extracted from the host cell through a variety of means well-known in the art. Such means include extraction with organic solvents,
15 sonication, supercritical fluid extraction using for example carbon dioxide, and physical means such as presses, or combinations thereof. Of particular interest is extraction with methanol and chloroform. Where appropriate, the aqueous layer can be acidified to protonate negatively charged moieties and thereby increase partitioning of desired products into the organic layer. After extraction, the organic solvents can be removed by evaporation under a stream of nitrogen.
20 When isolated in conjugated forms, the products are enzymatically or chemically cleaved to release the free fatty acid or a less complex conjugate of interest, and are then subjected to further manipulations to produce a desired end product. Desirably, conjugated forms of fatty acids are cleaved with potassium hydroxide.

If further purification is necessary, standard methods can be employed. Such methods
25 include extraction, treatment with urea, fractional crystallization, HPLC, fractional distillation, silica gel chromatography, high speed centrifugation or distillation, or combinations of these techniques. Protection of reactive groups, such as the acid or alkenyl groups, can be done at any step through known techniques, for example alkylation or iodination. Methods used include methylation of the fatty acids to produce methyl esters. Similarly, protecting groups can be
30 removed at any step. Desirably, purification of fractions containing DHA and EPA is accomplished by treatment with urea and/or fractional distillation.

The uses of the subject invention are several. Probes based on the DNAs of the present invention find use in methods for isolating related molecules or in methods to detect organisms expressing PKS-like genes. When used as probes, the DNAs or oligonucleotides need to be
35 detectable. This is usually accomplished by attaching a label either at an internal site, for example via incorporation of a modified residue, or at the 5' or 3' terminus. Such labels can be directly detectable, can bind to a secondary molecule that is detectably labeled, or can bind to an

unlabelled secondary molecule and a detectably labeled tertiary molecule; this process can be extended as long as is practicable to achieve a satisfactorily detectable signal without unacceptable levels of background signal. Secondary, tertiary, or bridging systems can include use of antibodies directed against any other molecule, including labels or other antibodies, or can involve any molecules which bind to each other, for example a biotin-streptavidin/avidin system. Detectable labels typically include radioactive isotopes, molecules which chemically or enzymatically produce or alter light, enzymes which produce detectable reaction products, magnetic molecules, fluorescent molecules or molecules whose fluorescence or light-emitting characteristics change upon binding. Examples of labelling methods can be found in USPN 5,011,770. Alternatively, the binding of target molecules can be directly detected by measuring the change in heat of solution on binding of a probe to a target via isothermal titration calorimetry, or by coating the probe or target on a surface and detecting the change in scattering of light from the surface produced by binding of a target or a probe, respectively, is done with the BIAcore system.

PUFAs produced by recombinant means find applications in a wide variety of areas. Supplementation of humans or animals with PUFAs in various forms can result in increased levels not only of the added PUFAs, but of their metabolic progeny as well. Complex regulatory mechanisms can make it desirable to combine various PUFAs, or to add different conjugates of PUFAs, in order to prevent, control or overcome such mechanisms to achieve the desired levels of specific PUFAs in an individual. In the present case, expression of PKS-like gene genes, or antisense PKS-like gene transcripts, can alter the levels of specific PUFAs, or derivatives thereof, found in plant parts and/or plant tissues. The PKS-like gene polypeptide coding region is expressed either by itself or with other genes, in order to produce tissues and/or plant parts containing higher proportions of desired PUFAs or containing a PUFA composition which more closely resembles that of human breast milk (Prieto *et al.*, PCT publication WO 95/24494) than does the unmodified tissues and/or plant parts.

PUFAs, or derivatives thereof, made by the disclosed method can be used as dietary supplements for patients undergoing intravenous feeding or for preventing or treating malnutrition. For dietary supplementation, the purified PUFAs, or derivatives thereof, can be incorporated into cooking oils, fats or margarines formulated so that in normal use the recipient receives a desired amount of PUFA. The PUFAs also can be incorporated into infant formulas, nutritional supplements or other food products, and find use as anti-inflammatory or cholesterol lowering agents.

Particular fatty acids such as EPA can be used to alter the composition of infant formulas to better replicate the PUFA composition of human breast milk. The predominant triglyceride in human milk is reported to be 1,3-di-oleoyl-2-palmitoyl, with 2-palmitoyl glycerides reported as better absorbed than 2-oleoyl or 2-lineoyl glycerides (*see* USPN 4,876,107). Typically, human

breast milk has a fatty acid profile comprising from about 0.15 % to about 0.36 % as DHA, from about 0.03 % to about 0.13 % as EPA, from about 0.30 % to about 0.88 % as ARA, from about 0.22 % to about 0.67 % as DGLA, and from about 0.27 % to about 1.04 % as GLA. A preferred ratio of GLA:DGLA:ARA in infant formulas is from about 1:1:4 to about 1:1:1, respectively.

- 5 Amounts of oils providing these ratios of PUFA can be determined without undue experimentation by one of skill in the art. PUFAs, or host cells containing them, also can be used as animal food supplements to alter an animal's tissue or milk fatty acid composition to one more desirable for human or animal consumption.

- 10 For pharmaceutical use (human or veterinary), the compositions generally are administered orally but can be administered by any route by which they may be successfully absorbed, e.g., parenterally (i.e. subcutaneously, intramuscularly or intravenously), rectally or vaginally or topically, for example, as a skin ointment or lotion. Where available, gelatin capsules are the preferred form of oral administration. Dietary supplementation as set forth above also can provide an oral route of administration. The unsaturated acids of the present invention can be administered in conjugated forms, or as salts, esters, amides or prodrugs of the fatty acids. Any pharmaceutically acceptable salt is encompassed by the present invention; especially preferred are the sodium, potassium or lithium salts. Also encompassed are the N-alkylpolyhydroxamine salts, such as N-methyl glucamine, described in PCT publication WO 96/33155. Preferred esters are the ethyl esters.

- 20 The PUFAs of the present invention can be administered alone or in combination with a pharmaceutically acceptable carrier or excipient. As solid salts, the PUFAs can also be administered in tablet form. For intravenous administration, the PUFAs or derivatives thereof can be incorporated into commercial formulations such as Intralipids. Where desired, the individual components of formulations can be individually provided in kit form, for single or multiple use. A typical dosage of a particular fatty acid is from 0.1 mg to 20 g, or even 100 g daily, and is preferably from 10 mg to 1, 2, 5 or 10 g daily as required, or molar equivalent amounts of derivative forms thereof. Parenteral nutrition compositions comprising from about 2 to about 30 weight percent fatty acids calculated as triglycerides are encompassed by the present invention. Other vitamins, and particularly fat-soluble vitamins such as vitamin A, D, E and L-carnitine optionally can be included. Where desired, a preservative such as a tocopherol can be added, typically at about 0.1% by weight.

The following examples are presented by way of illustration, not of limitation.

EXAMPLESExample 1The Identity of ORFs Derived from *Vibrio marinus*

5 Using polymerase chain reaction (PCR) with primers based on ORF 6 of *Shewanella* (Sp ORF 6) sequences (FW 5' primers CUACUACUACUACCAAGCT
AAAGCACTTAACCGTG, SEQ ID NO:41, and CUACUACUACUACAGCGAAATG
CTTATCAAG, SEQ ID NO:42, for *Vibrio* and SS9 respectively and 3' BW primers:
CAUCAUCAUCAUGCGACCAAAACCAAATGAGCTAATAC, SEQ ID NO:43, for both
10 *Vibrio* and SS9) and genomic DNAs templates from *Vibrio* and a borophyllic *photobacter*
producing EPA (provided by Dr. Bartlett, UC San Diego), resulted in PCR products of *ca.*400
bases for *Vibrio marinus* (*Vibrio*) and *ca.*900 bases for SS9 presenting more than 75% homology
with corresponding fragments of Sp ORF 6 (*see* Figure 25) as determined by direct counting of
homologous amino acids.

15 A *Vibrio* cosmid library was then prepared and using the *Vibrio* ORF 6 PCR product as a
probe (*see* Figure 26); clones containing at least ORF 6 were selected by colony hybridization.

Through additional sequences of the selected cosmids such as cosmid #9 and cosmid
#21, a *Vibrio* cluster (Figure 5) with ORFs homologous to, and organized in the same sequential
order (ORFs 6-9) as ORFs 6-9 of *Shewanella*, was obtained (Figure 7). The *Vibrio* ORFs from
20 this sequence are found at 17394 to 36115 and comprehend ORFs 6-9.

Table*Vibrio* operon figures

	17394 to 25349	length = 7956 nt
25	25509 to 28157	length = 2649 nt
	28209 to 34262	length = 6054 nt
	34454 to 36115	length = 1662 nt

The ORF designations for the *Shewanella* genes are based on those disclosed in Figure 4, and
30 differ from those published for the *Shewanella* cluster (Yazawa *et al*, USPN 5,683,898). For
instance, ORF 3 of Figure 4 is read in the opposite direction from the other ORFs and is not
disclosed in Yazawa *et al* USPN 5,683,898 (See Fig. 24) for comparison with Yazawa *et al*
USPN 5,683,898.

Sequences homologous to ORF 3, were not found in the proximity of ORF 6 (17000
35 bases upstream of ORF 6) or of ORF 9 (*ca.*4000 bases downstream of ORF 9). Motifs
characteristic of phosphopantethenyl transferases (Lambalot *et al* (1996) *Current Biology* 3:923-

936) were absent from the *Vibrio* sequences screened for these motifs. In addition, there was no match to *Sp* ORF 3 derived probes in genomic digests of *Vibrio* and of SC2A *Shewanella* (another bacterium provided by the University of San Diego and also capable of producing EPA). Although ORF 3 may exist in *Vibrio*, its DNA may not be homologous to that of *Sp* ORF 3 and/or could be located in portions of the genome that were not sequenced.

Figure 6 provides the sequence of an approximately 19 kb *Vibrio* clone comprising ORFs 6-9. Figures 7 and 8 compare the gene cluster organizations of the PKS-like systems of *Vibrio marinus* and *Shewanella putrefaciens*. Figures 9 through 12 show the levels of sequence homology between the corresponding ORFs 6, 7, 8 and 9, respectively.

Example 2

ORF 8 Directs DHA Production

As described in example 1, DNA homologous to *Sp* ORF 6 was found in an unrelated species, SS9 *Photobacter*, which also is capable of producing EPA. Additionally, ORFs homologous to *Sp* ORF 6-9 were found in the DHA producing *Vibrio marinus* (*Vibrio*). From these ORFs a series of experiments was designed in which deletions in each of *Sp* ORFs 6-9 that suppressed EPA synthesis in *E. coli* (Yazawa (1996) *supra*) were complemented by the corresponding homologous genes from *Vibrio*.

The *Sp* EPA cluster was used to determine if any of the *Vibrio* ORFs 6-9 was responsible for the production of DHA. Deletion mutants provided for each of the *Sp* ORFs are EPA and DHA null. Each deletion was then complemented by the corresponding *Vibrio* ORF expressed behind a *lac* promoter (Figure 13).

The complementation of a *Sp* ORF 6 deletion by a *Vibrio* ORF 6 reestablished the production of EPA. Similar results were obtained by complementing the *Sp* ORF 7 and ORF 9 deletions. By contrast, the complementation of a *Sp* ORF 8 deletion resulted in the production of C22:6. *Vibrio* ORF 8 therefore appears to be a key element in the synthesis of DHA. Figures 14 and 15 show chromatograms of fatty acid profiles from the respective complementations of *Sp* del ORF 6 with *Vibrio* ORF 6 (EPA and no DHA) and *Sp* del ORF 8 with *Vibrio* ORF 8 (DHA). Figure 16 shows the fatty acid percentages for the ORF 8 complementation, again demonstrating that ORF 8 is responsible for DHA production.

These data show that polyketide-like synthesis genes with related or similar ORFs can be combined and expressed in a heterologous system and used to produce a distinct PUFA species in the host system, and that ORF 8 has a role in determining the ultimate chain length. The *Vibrio* ORFs 6, 7, 8, and 9 reestablish EPA synthesis. In the case of *Vibrio* ORF 8, DHA is also present (*ca.* 0.7%) along with EPA (*ca.* 0.6%) indicating that this gene plays a significant role in directing synthesis of DHA vs EPA for these systems.

Example 3Requirements for Production of DHA

To determine how *Vibrio* ORFs of the cluster ORF 6-9 are used in combination with *Vibrio* ORF 8, some combinations of *Vibrio* ORF 8 with some or all of the other *Vibrio* ORFS 6-9 cluster were created to explain the synthesis of DHA.

Vibrio ORFs 6-9 were complemented with *Sp* ORF 3. The results of this complementation are presented in Figures 16b and 16c. The significant amounts of DHA measured (greater than about 9%) and the absence of EPA suggest that no ORFs other than those of *Vibrio* ORFs 6-9 are required for DHA synthesis when combined with *Sp* ORF 3. This suggests that *Sp* ORF 3 plays a general function in the synthesis of bacterial PUFAs.

With respect to the DHA vs EPA production, it may be necessary to combine *Vibrio* ORF 8 with other *Vibrio* ORFs of the 6-9 cluster in order to specifically produce DHA. The roles of *Vibrio* ORF 9 and each of the combinations of *Vibrio* ORFs (6,8), (7, 8), (8, 9), etc in the synthesis of DHA are being studied.

Example 4Plant Expression Constructs

A cloning vector with very few restriction sites was designed to facilitate the cloning of large fragments and their subsequent manipulation. An adapter was assembled by annealing oligonucleotides with the sequences AAGCCCGGGCTT, SEQ ID NO:44, and GTACAAGCCCGGGCTTAGCT, SEQ ID NO:45. This adapter was ligated to the vector pBluescript II SK+ (Stratagene) after digestion of the vector with the restriction endonucleases *Asp718* and *SstI*. The resulting vector, pCGN7769 had a single *SrfI* (and embedded *SmaI*) cloning site for the cloning of blunt ended DNA fragments.

A plasmid containing the napin cassette from pCGN3223, (USPN 5,639,790) was modified to make it more useful for cloning large DNA fragments containing multiple restriction sites, and to allow the cloning of multiple napin fusion genes into plant binary transformation vectors. An adapter comprised of the self annealed oligonucleotide of sequence CGCGATTAAATGGCGCGCCCTGCAGGCGCCGCCTGCAGGGCGC GCCATTAAAT, SEQ ID NO:46, was ligated into the vector pBC SK+ (Stratagene) after digestion of the vector with the restriction endonuclease *BssHII* to construct vector pCGN7765. Plasmids pCGN3223 and pCGN7765 were digested with *NotI* and ligated together. The resultant vector, pCGN7770 (Figure 17), contains the pCGN7765 backbone and the napin seed specific expression cassette from pCGN3223.

Shewanella constructs

Genes encoding the *Shewanella* proteins were mutagenized to introduce suitable cloning sites 5' and 3' ORFs using PCR. The template for the PCR reactions was DNA of the cosmid pEPA (Yazawa *et al, supra*). PCR reactions were performed using Pfu DNA polymerase according to the manufacturers' protocols. The PCR products were cloned into *SrfI* digested pCGN7769. The primers CTGCAGCTCGAGACAATGTTGATT
 5 TCCTTATACTTCTGTCC, SEQ ID NO:47, and GGATCCAGATCTCTAGCTAGTC
 TTAGCTGAAGCTCGA, SEQ ID NO:48, were used to amplify ORF 3, and to generate plasmid pCGN8520. The primers TCTAGACTCGAGACAATGAGCCAGACCTC
 TAAACCTACA, SEQ ID NO:49, and CCCGGGCTCGAGCTAATTCGCCTCACTGTC
 10 GTTTGCT, SEQ ID NO:50, were used to amplify ORF 6, and generate plasmid pCGN7776. The primers GAATTCCTCGAGACAATGCCGCTGCGCATCG
 CACTTATC, SEQ ID NO: 51, and GGTACCAGATCTTTAGACTTCCCCTTGAAG
 TAAATGG, SEQ ID NO:52, were used to amplify ORF 7, and generate plasmid pCGN7771. The primers GAATTCGTCGACACAATGTCATTACCAGACAATGC
 15 TTCT, SEQ ID NO:53, and TCTAGAGTCGACTTATACAGATTCTTCGATGCT
 GATAG, SEQ ID NO:54, were used to amplify ORF 8, and generate plasmid pCGN7775. The primers GAATTCGTCGACACAATGAATCCTACAGCAACTAACGAA, SEQ ID NO:55, and
 TCTAGAGGATCCTTAGGCCATTCTTTGGTTTGGCTTC, SEQ ID NO:56, were used to amplify ORF 9, and generate plasmid pCGN7773.

20 The integrity of the PCR products was verified by DNA sequencing of the inserts of pCGN7771, pCGN8520, and pCGN7773. ORF 6 and ORF 8 were quite large in size. In order to avoid sequencing the entire clones, the center portions of the ORFs were replaced with restriction fragments of pEPA. The 6.6 kilobase *PacI/BamHI* fragment of pEPA containing the central portion of ORF 6 was ligated into *PacI/BamHI* digested pCGN7776 to yield
 25 pCGN7776B4. The 4.4 kilobase *BamHI/BglII* fragment of pEPA containing the central portion of ORF 8 was ligated into *BamHI/BglII* digested pCGN7775 to yield pCGN7775A. The regions flanking the pEPA fragment and the cloning junctions were verified by DNA sequencing.

Plasmid pCGN7771 was cut with *XhoI* and *BglII* and ligated to pCGN7770 after digestion with *SaII* and *BglII*. The resultant napin/ORF 7 gene fusion plasmid was designated
 30 pCGN7783. Plasmid pCGN8520 was cut with *XhoI* and *BglII* and ligated to pCGN7770 after digestion with *SaII* and *BglII*. The resultant napin/ORF 3 gene fusion plasmid was designated pCGN8528. Plasmid pCGN7773 was cut with *SaII* and *BamHI* and ligated to pCGN7770 after digestion with *SaII* and *BglII*. The resultant napin/ORF 9 gene fusion plasmid was designated pCGN7785. Plasmid pCGN7775A was cut with *SaII* and ligated to pCGN7770 after digestion
 35 with *SaII*. The resultant napin/ORF 8 gene fusion plasmid was designated pCGN7782. Plasmid pCGN7776B4 was cut with *XhoI* and ligated to pCGN7770 after digestion with *SaII*. The resultant napin/ORF 6 gene fusion plasmid was designated pCGN7786B4.

A binary vector for plant transformation, pCGN5139, was constructed from pCGN1558 (McBride and Summerfelt (1990) *Plant Molecular Biology*, 14:269-276). The polylinker of pCGN1558 was replaced as a *HindIII*/*Asp718* fragment with a polylinker containing unique restriction endonuclease sites, *Ascl*, *PacI*, *XbaI*, *SwaI*, *BamHI*, and *NotI*. The *Asp718* and *HindIII* restriction endonuclease sites are retained in pCGN5139. pCGN5139 was digested with *NotI* and ligated with *NotI* digested pCGN7786B4. The resultant binary vector containing the napin/ORF 6 gene fusion was designated pCGN8533. Plasmid pCGN8533 was digested with *Sse8387I* and ligated with *Sse8387I* digested pCGN7782. The resultant binary vector containing the napin/ORF 6 gene fusion and the napin/ORF 8 gene fusion was designated pCGN8535 (Figure 18).

The plant binary transformation vector, pCGN5139, was digested with *Asp718* and ligated with *Asp718* digested pCGN8528. The resultant binary vector containing the napin/ORF 3 gene fusion was designated pCGN8532. Plasmid pCGN8532 was digested with *NotI* and ligated with *NotI* digested pCGN7783. The resultant binary vector containing the napin/ORF 3 gene fusion and the napin/ORF 7 gene fusion was designated pCGN8534. Plasmid pCGN8534 was digested with *Sse8387I* and ligated with *Sse8387I* digested pCGN7785. The resultant binary vector containing the napin/ORF 3 gene fusion, the napin/ORF 7 gene fusion and the napin/ORF 9 gene fusion was designated pCGN8537 (Figure 19).

20 Vibrio constructs

The *Vibrio* ORFs for plant expression were all obtained using *Vibrio* cosmid #9 as a starting molecule. *Vibrio* cosmid #9 was one of the cosmids isolated from the *Vibrio* cosmid library using the *Vibrio* ORF 6 PCR product described in Example 1.

A gene encoding *Vibrio* ORF 7 (Figure 6) was mutagenized to introduce a *SalI* site upstream of the open reading frame and *BamHI* site downstream of the open reading frame using the PCR primers: TCTAGAGTCGACACAATGGCGGAATTAGCTG TTATTGGT, SEQ ID NO:57, and GTCGACGGATCCCTATTTGTTCTGTTTGCTA TATG, SEQ ID NO:58. A gene encoding *Vibrio* ORF 9 (Figure 6) was mutagenized to introduce a *BamHI* site upstream of the open reading frame and an *XhoI* site downstream of the open reading frame using the PCR primers: GTCGACGGATCCA CAATGAATATAGTAAGTAATCATTCGGCA, SEQ ID NO:59, and GTCGACCTC GAGTTAATCACTCGTACGATAACTTGCC, SEQ ID NO:60. The restriction sites were introduced using PCR, and the integrity of the mutagenized plasmids was verified by DNA sequence. The *Vibrio* ORF 7 gene was cloned as a *SalI*-*BamHI* fragment into the napin cassette of *Sal*-*BglI* digested pCGN7770 (Figure 17) to yield pCGN8539. The *Vibrio* ORF 9 gene was cloned as a *SalI*-*BamHI* fragment into the napin cassette of *Sal*-*BalI* digested pCGN7770 (Figure 17) to yield pCGN8543.

Genes encoding the *Vibrio* ORF 6 and ORF 8 were mutagenized to introduce *Sa*I sites flanking the open reading frames. The *Sa*I sites flanking ORF 6 were introduced using PCR. The primers used were: CCCGGGTCGACACAATGGCTAAAAAGAACA CCACATCGA, SEQ ID NO:61, and CCCGGGTCGACTCATGACATATCGTTCAAA ATGTCCTGA, SEQ ID NO:62. The central 7.3 kb *Bam*HI-*Xho*I fragment of the PCR product was replaced with the corresponding fragment from *Vibrio* cosmid #9. The mutagenized ORF 6 were cloned into the *Sa*I site of the napin cassette of pCGN7770 to yield plasmid pCGN8554.

The mutagenesis of ORF 8 used a different strategy. A *Bam*HI fragment containing ORF 8 was subcloned into plasmid pH79 to yield cosmid #9". A *Sa*I site upstream of the coding region was introduced on and adapter comprised of the oligonucleotides TCGACATGGAAAATATTGCAGTAGTAGGTATTGCTAATTT GTTC, SEQ ID NO:63, and CCGGGAACAAATTAGCAATACCTACTACTGCAAT ATTTTCCATG, SEQ ID NO:64. The adapter was ligated to cosmid #9" after digestion with *Sa*I and *Xma*I. A *Sa*I site was introduced downstream of the stop codon by using PCR for mutagenesis. A DNA fragment containing the stop codon was generated using cosmid #9" as a template with the primers TCAGATGAACTTTATCGATAC, SEQ ID NO:65 and TCATGAGACGTCGTCGACTTACGCTTCAACAATACT, SEQ ID NO:66. The PCR product was digested with the restriction endonucleases *Cla*I and *Aat*II and was cloned into the cosmid 9" derivative digested with the same enzymes to yield plasmid 8P3. The *Sa*I fragment from 8P3 was cloned into *Sa*I digested pCGN7770 to yield pCGN8515.

pCGN8532, a binary plant transformation vector that contains a *Shewannella* ORF 3 under control of the napin promoter was digested with *Not*I, and a *Not*I fragment of pCGN8539 containing a napin *Vibrio* ORF 7 gene fusion was inserted to yield pCGN8552. Plasmid pCGN8556 (Figure 23), which contains *Shewannella* ORF 3, and *Vibrio* ORFs 7 and 9 under control of the napin promoter was constructed by cloning the *Sse*8357 fragment from pCGN8543 into *Sse*8387 digested pCGN8552.

The *Not*I digested napin/ORF 8 gene from plasmid pCGN8515 was cloned into a *Not*I digested plant binary transformation vector pCGN5139 to yield pCGN8548. The *Sse*8387 digested napin/ORF 6 gene from pCGN8554 was subsequently cloned into the *Sse*8387 site of pCGN8566. The resultant binary vector containing the napin/ORF 6 gene fusion and napin/ORF 8 gene fusion was designated pCGN8560 (Figure 22).

Example 5

Plant Transformation and PUFA Production

EPA production

The *Shewanella* constructs pCGN8535 and pCGN8537 can be transformed into the same or separate plants. If separate plants are used, the transgenic plants can be crossed resulting in heterozygous seed which contains both constructs.

pCGN8535 and pCGN8537 are separately transformed into *Brassica napus*. Plants are
5 selected on media containing kanamycin and transformation by full length inserts of the constructs is verified by Southern analysis. Immature seeds also can be tested for protein expression of the enzyme encoded by ORFs 3, 6, 7, 8, or 9 using western analysis, in which case, the best expressing pCGN8535 and pCGN8537 T₁ transformed plants are chosen and are grown out for further experimentation and crossing. Alternatively, the T₁ transformed plants
10 showing insertion by Southern are crossed to one another producing T₂ seed which has both insertions. In this seed, half seeds may be analyzed directly from expression of EPA in the fatty acid fraction. Remaining half-seed of events with the best EPA production are grown out and developed through conventional breeding techniques to provide *Brassica* lines for production of EPA.

15 Plasmids pCGN7792 and pCGN7795 also are simultaneously introduced into *Brassica napus* host cells. A standard transformation protocol is used (*see* for example USPN 5,463,174 and USPN 5,750,871, however *Agrobacteria* containing both plasmids are mixed together and incubated with *Brassica* cotyledons during the cocultivation step. Many of the resultant plants are transformed with both plasmids.

20

DHA production

A plant is transformed for production of DHA by introducing pCGN8556 and pCGN8560, either into separate plants or simultaneously into the same plants as described for EPA production.

25 Alternatively, the *Shewanella* ORFs can be used in a concerted fashion with ORFs 6 and 8 of *Vibrio*, such as by transforming with a plant the constructs pCGN8560 and pCGN7795, allowing expression of the corresponding ORFs in a plant cell. This combination provides a PKS-like gene arrangement comprising ORFs 3, 7 and 9 of *Shewanella*, with an ORF 6 derived from *Vibrio* and also an ORF 8 derived from *Vibrio*. As described above, ORF 8 is the PKS-like
30 gene which controls the identity of the final PUFA product. Thus, the resulting transformed plants produce DHA in plant oil.

Example 6

Transgenic plants containing the *Shewanella* PUFA genes

35 *Brassica* plants

Fifty-two plants cotransformed with plasmids pCGN8535 and pCGN8537 were analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Forty-one plants contained plasmid pCGN8537, and thirty-five plants contained pCGN8535. 11 of the plants contained all five ORFs required for the synthesis of EPA. Several plants contained genes from both of the binary plasmids but appeared to be missing at least one of the ORFs. Analysis is currently being performed on approximately twenty additional plants.

Twenty-three plants transformed with pCGN8535 alone were analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Thirteen of these plants contained both *Shewanella* ORF 6 and *Shewanella* ORF 8. Six of the plants contained only one ORF.

Nineteen plants transformed with pCGN8537 were alone analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Eighteen of the plants contained *Shewanella* ORF 3, *Shewanella* ORF 7, and *Shewanella* ORF 9. One plant contained *Shewanella* ORFs 3 and 7.

Arabidopsis

More than 40 transgenic *Arabidopsis* plants cotransformed with plasmids pCGN8535 and pCGN8537 are growing in our growth chambers. PCR analysis to determine which of the ORFs are present in the plants is currently underway.

Example 7

Evidence of A PKS System of PUFA Synthesis In *Schizochytrium*

The purpose of this experiment was to identify additional sources of PKS genes. Polyunsaturated long chain fatty acids were identified in *Schizochytrium* oil. Furthermore, production of polyunsaturated fatty acids was detected in a culture of *Schizochytrium*. A freshly diluted culture of *Schizochytrium* was incubated at 24°C in the presence of [¹⁴C]-acetate (5uCi/mL) for 30 min with shaking (150 rpm). The cells were then collected by centrifugation, lyophilized and subjected to a transesterification protocol that involved heating to 90°C for 90 minutes in the presence of acidic (9% H₂SO₄) methanol with toluene (1 volume of toluene per two volumes of acidic methanol) as a second solvent. The resulting methylesters were extracted with an organic solvent (hexane) and separated by TLC (silica gel G, developed three times with hexane:diethyl ether (19:1)). Radioactivity on the TLC plate was detected using a scanner (AMBIS). Two prominent bands were detected on the TLC plate. These bands migrated on the TLC plate in positions expected for short chain (14 to 16 carbon), saturated methyl esters (the upper band) and with methylesters of polyunsaturated long chain (20 to 22 carbon) fatty acids (the lower band). These were also the major types of fatty acids detected by GC analysis of FAMES of *Schizochytrium* oil.

In a parallel experiment thiolactomycin, a well known inhibitor of Type II fatty acid synthesis systems as well as several polyketide synthesis systems including EPA production by *E. coli* transformed with PKS genes derived from *Shewanella*, was added to the test tubes of varying concentrations (0, 1, 10 and 100 µg/ml) prior to addition of the *Schizochytrium* cell cultures and [¹⁴C] acetate. Analysis of incorporation of [¹⁴C] acetate, as described above, revealed that 100 ug/mL thiolactomycin completely blocked synthesis of polyunsaturated fatty acids, while partial inhibition of synthesis of polyunsaturated fatty acids was observed at 10 ug/mL thiolactomycin. Synthesis of the short chain saturated fatty acids was unaffected at all tested thiolactomycin concentrations. Thiolactomycin does not inhibit Type I fatty acid synthesis systems and is not toxic to mice, suggesting that it does not inhibit the elongation system leading to EPA or DHA formation. Furthermore, thiolactomycin did not inhibit the elongation system leading to PUFA synthesis in *Phaeodactylum tricornutum*. Therefore, although *Schizochytrium* is known to possess a Type I fatty acid synthesis system, the data suggested that the polyunsaturated fatty acids produced in this organism were derived from a system which was distinct from the Type I fatty acid synthesis system which produced short chain fatty acids, and from a system that was similar to the elongation/desaturation pathway found in mice and *Phaeodactylum*. The data are consistent with DHA formation being a result of a PKS pathway as found in *Vibrio marinus* and *Shewanella putrefaciens*.

Example 8

PKS Related Sequences From *Schizochytrium*

The purpose of this experiment was to identify sequences from *Schizochytrium* that encoded PKS genes. A cDNA library from *Schizochytrium* was constructed and approximately 8,000 random clones (ESTs) were sequenced. The protein sequence encoded by *Shewanella* EPA synthesis genes was compared to the predicted amino acid sequences of the *Schizochytrium* ESTs using a Smith/Waterman alignment algorithm. When the protein sequence of ORF6 (*Shewanella*) was compared with the amino acid sequences from *Schizochytrium* ESTs, 38 EST clones showed a significant degree of identity ($P < 0.01$). When the protein sequence of ORF7 was compared by *Schizochytrium* ESTs, 4 EST clones showed significant identity ($P < 0.01$) suggesting that the molecules were homologous. When the protein sequence of ORF8 and ORF9 were compared with the *Schizochytrium* ESTs, 7 and 14 clones respectively showed significant identity ($P < 0.01$).

Example 9

Analysis of *Schizochytrium* cDNA Clones

Restriction enzyme analysis of the *Schizochytrium* EST clones was used to determine the longest clones, which were subsequently sequenced in their entirety. All of the EST sequences described in Example 8 were determined to be part of 5 cDNA clones.

Two of the cDNA clones were homologous to *Shewanella* ORF6. LIB3033-047-B5 was
5 homologous to the C-terminus of ORF6. The sequence of LIB3033-047-B5 could be aligned with *Shewanella* ORF6 from amino acids 2093 onwards. The open reading frame of LIB3033-047-B5 extended all the way to the 5' end of the sequence, thus this clone was not likely to be full length. LIB3033-046-E6 shared homology to the ACP domain of ORF6. It contained 6
10 ACP repeats. This cDNA clone did not have a poly-A-tail, and therefore, it was likely to be a partial cDNA with additional regions of the cDNA found downstream of the sequence. The PCR primers GTGATGATCTTTCCCTGATGCACGCCAAGG (SEQ ID NO: 67) and AGCTCGAGACCGGCAACCCGCAGCGCCAGA (SEQ ID NO: 68) were used to amplify a fragment of approximately 500 nucleotides from *Schizochytrium* genomic DNA. Primer
15 GTGATGATCTTTCCCTGATGCACGCCAAGG was derived from LIB3033-046-E6, and primer AGCTCGAGACCGGCAACCCGCAGCGCCAGA was derived from LIB3033-047-B5. Thus, LIB3033-046-E6 and LIB3033-047-B5 represented different portions of the same mRNA (see Figure 28) and could be assembled into a single partial cDNA sequence (see Figure 27A),
20 SEQ ID NO: 69, that was predicted to encode a protein with the sequence in Figure 29A (SEQ ID NO: 70). The open reading frame extended all the way to the 5' end of the sequence, thus this partial cDNA was not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by clones LIB3033-046-E6 and LIB3033-047-B5. It may contain condensing enzyme related domains similar to those found near the N-terminus of *Shewanella* ORF6.

One of the cDNA clones, LIB3033-046-D2, was homologous to *Shewanella* ORF9 at its
25 3' end. This clone was homologous to the chain length factor region of *Shewanella* ORF8 at its 5' end. This clone was also homologous to the entire open reading frame of the *Anabaena* HglC ORF. The *Anabaena* HglC ORF is homologous to the chain length factor region of *Shewanella* ORF8 and *Shewanella* ORF7. Thus this cDNA (Figure 27B), SEQ ID NO: 71, was homologous to part of *Shewanella* ORF8, *Shewanella* ORF7 and *Shewanella* ORF9 (see Figure 28). The
30 amino acid sequence (Figure 29B), SEQ ID NO: 72, encoded by the open reading frame of LIB3033-046-D2 extended all the way to the 5' end of the sequence; thus this clone was not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by LIB3033-046-E6. It may contain condensing enzyme related domains similar to those found near the N-terminus of *Shewanella*
35 ORF8.

Two additional cDNA clones were homologous to *Shewanella* ORF8. LIB81-015-D5 was homologous to the C-terminus of ORF8. The 5' sequence of LIB81-015-D5 could be

aligned with *Shewanella* ORF8 from amino acids 1900 onwards. The 3' end of LIB81-015-D5 could be aligned with *Shewanella* ORF9 (see Figure 28). The amino acid sequence (Figure 29C), SEQ ID NO: 73, encoded by the open reading frame of LIB81-015-D5 extended all the way to the 5' end of the sequence; thus this clone was not likely to be full length. LIB81-042-B9 was homologous to amino acids 1150 to 1850 of *Shewanella* ORF8. LIB81-042-B9 did not have a poly-A-tail, and therefore, it was likely to be a partial cDNA with additional regions of the cDNA found downstream of the sequence. The PCR primers TACCGCGGCAAGACTATCCGCAACGTCACC (SEQ ID NO: 74) and GCCGTCGTGGGCGTCCACGGACACGATGTG (SEQ ID NO: 75) were used to amplify a fragment of approximately 500 nucleotides from *Schizochytrium* genomic DNA. Primer TACCGCGGCAAGACTATCCGCAACGTCACC was derived from LIB81-042-B9, and primer GCCGTCGTGGGCGTCCACGGACACGATGTG was derived from LIB81-015-D5. Thus, LIB81-042-and LIB81-015-D5 represented different portions of the same mRNA and were assembled into a single partial cDNA sequence (see Figure 27C), SEQ ID NO: 76. The open reading frame of LIB81-042-B9 also extended all the way to the 5' end of the sequence, thus this clone was also not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by LIB81-042-B9.

By the present invention PKS-like genes from various organisms can now be used to transform plant cells and modify the fatty acid compositions of plant cell membranes or plant seed oils through the biosynthesis of PUFAs in the transformed plant cells. Due to the nature of the PKS-like systems, fatty acid end-products produced in the plant cells can be selected or designed to contain a number of specific chemical structures. For example, the fatty acids can comprise the following variants: Variations in the numbers of keto or hydroxyl groups at various positions along the carbon chain; variations in the numbers and types (*cis* or *trans*) of double bonds; variations in the numbers and types of branches off of the linear carbon chain (methyl, ethyl, or longer branched moieties); and variations in saturated carbons. In addition, the particular length of the end-product fatty acid can be controlled by the particular PKS-like genes utilized.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. An isolated nucleic acid comprising:
a *Vibrio marinus* nucleotide sequence selected from the group consisting of ORF 6 (SEQ ID NO:77), ORF 7 (SEQ ID NO:78), ORF 8 (SEQ ID NO:79), and ORF 9 (SEQ ID NO:80), as
5 shown in Figure 6.
2. An isolated nucleic acid comprising:
a nucleotide sequence which encodes a polypeptide of a polyketide-like synthesis
system, wherein said system produces a docosahexenoic acid when expressed in a host cell.
10
3. The isolated nucleic acid according to Claim 2, wherein said nucleotide sequence is
derived from a marine bacterium.
4. An isolated nucleic acid according to Claim 2, wherein said nucleotide sequence is
15 derived from *Schizochytrium*.
5. The isolated nucleic acid according to Claim 2, wherein said nucleotide sequence is a
Vibrio marinus ORF 8 (SEQ ID NO:79), as shown in Figure 6.
- 20 6. An isolated nucleic acid comprising a *Schizochytrium* nucleotide sequence comprising a
sequence shown in a SEQ ID NO selected from the group consisting of SEQ ID NOS: 69, 71
and 76.
7. An isolated nucleic acid comprising:
25 a nucleotide sequence which is substantially identical to a sequence of at least 50
nucleotides of a *Vibrio marinus* nucleotide sequence selected from the group consisting of ORF
6 (SEQ ID NO:77), ORF 7 (SEQ ID NO:78), ORF 8 (SEQ ID NO:79), and ORF 9 (SEQ ID
NO:80), as shown in Figure 6.
- 30 8. A recombinant microbial cell comprising at least one copy of an isolated nucleic acid
according to Claim 6.
9. The recombinant microbial cell according to Claim 8, wherein said cell comprises each
element of a polyketide-like synthesis system required to produce a long chain polyunsaturated
35 fatty acid.

10. The recombinant microbial cell according to Claim 9, wherein said cell is a eukaryotic cell.
11. The recombinant microbial cell according to Claim 10, wherein said eukaryotic cell is a
5 fungal cell, an algae cell or an animal cell.
12. The recombinant microbial cell according to Claim 11, wherein said fungal cell is a yeast cell and said algae cell is a marine algae cell.
- 10 13. The recombinant microbial cell according to Claim 8, wherein said cell is a prokaryotic cell.
14. The recombinant microbial cell according to Claim 13, wherein said cell is a bacterial cell or a cyanobacterial cell.
- 15 15. A recombinant cell according to Claim 14, wherein said bacterial cell is a *lactobacillus* cell.
16. The microbial cell according to Claim 8, wherein said recombinant microbial cell is
20 enriched for 22:6 fatty acids as compared to a non-recombinant microbial cell which is devoid of said isolated nucleic acid.
17. A method for production of docosahexenoic acid in a microbial cell culture, said method comprising:
25 growing a microbial cell culture having a plurality of microbial cells, wherein said microbial cells or ancestors of said microbial cells were transformed with a vector comprising one or more nucleic acids having a nucleotide sequence which encodes a polypeptide of a polyketide synthesizing system, wherein said one or more nucleic acids are operably linked to a promoter, under conditions whereby said one or more nucleic acids are expressed and
30 docosahexenoic acid is produced in said microbial cell culture.
18. A method for production of a long chain polyunsaturated fatty acid in a plant cell, said method comprising:
growing a plant having a plurality of plant cells, wherein said plant cells or ancestors of
35 said plant cells were transformed with a vector comprising one or more nucleic acids having a nucleotide sequence which encodes one or more polypeptides of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid, wherein each of said nucleic

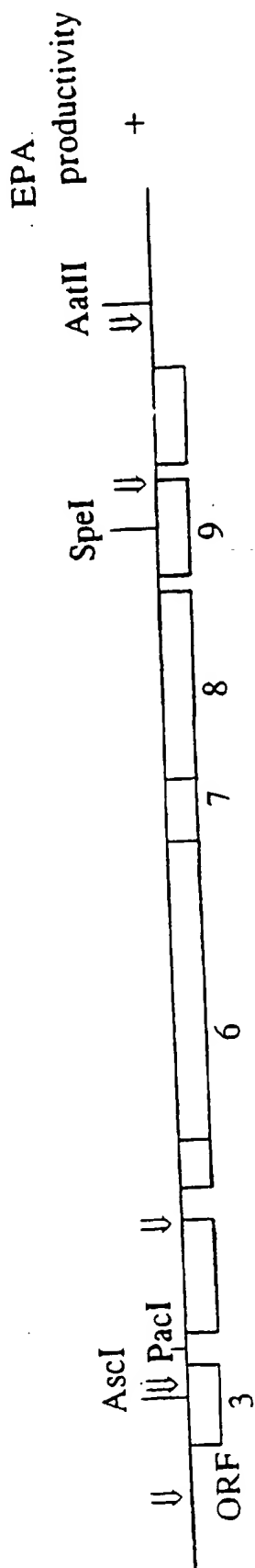
acids are operably linked to a promoter functional in a plant cell, under conditions whereby said polypeptides are expressed and a long chain polyunsaturated fatty acid is produced in said plant cells.

- 5 19. The method according to Claim 17 or Claim 18 wherein said nucleotide sequence is shown in a SEQ ID NO selected from the group consisting of SEQ ID NOS: 69, 71 and 76.
20. The method according to Claim 18, wherein said long chain polyunsaturated fatty acid produced in said plant cells is a 20:5 and 22:6 fatty acid.
- 10 21. The method according to Claim 17, wherein said nucleotide sequence is selected from the group consisting of *Vibrio marinus* ORF 6 (SEQ ID NO:77), ORF 7 (SEQ ID NO:78), ORF 8 (SEQ ID NO:79), and ORF 9 (SEQ ID NO:80), as shown in Figure 6 and *Shewanella putrefaciens* ORF 6 (SEQ ID NO:83), ORF 7 (SEQ ID NO:84), ORF 8 (SEQ ID NO:85), ORF 9 (SEQ ID NO:86), and ORF 3, which is complementary to SEQ ID NO:4, as shown in Figure 4.
- 15 22. The method according to Claim 18, wherein said nucleic acid constructs are derived from two or more polyketide synthesizing systems.
- 20 23. The method according to Claim 18, wherein said long chain polyunsaturated fatty acid is eicosapentenoic acid.
24. The method according to Claim 18, wherein said long chain polyunsaturated fatty acid is docosahexenoic acid.
- 25 25. A recombinant plant cell comprising:
one or more nucleic acids having a nucleotide sequence which encodes one or more polypeptides of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid, wherein each of said nucleic acids are operably linked to a promoter functional in said
30 plant cell.
26. The recombinant plant cell according to Claim 25, wherein said nucleotide sequence is shown in a SEQ ID NO selected from the group consisting of SEQ ID NOS: 69, 71 and 76.
- 35 27. The recombinant plant cell according to Claim 26, wherein said recombinant plant cell is a recombinant seed cell.

28. The recombinant plant cell according to Claim 27, wherein said recombinant seed cell is a recombinant embryo cell.
29. The recombinant plant cell according to Claim 26, wherein said recombinant plant cell is
5 from a plant selected from the group consisting of *Brassica*, soybean, safflower, and sunflower.
30. A plant oil produced by a recombinant plant cell according to Claim 26.
31. The plant oil according to Claim 30, wherein said plant oil comprises eicosapentenoic
10 acid.
32. The plant oil according to Claim 30, wherein said plant oil comprises docosahexenoic acid.
33. The plant oil according to Claim 30, wherein said plant oil is encapsulated.
15
34. A dietary supplement comprising a plant oil according to Claim 30.
35. A recombinant *E. coli* cell comprising:
20 one or more nucleic acids having a nucleotide sequence which encodes one or more polypeptides of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid, wherein each of said nucleic acids are operably linked to a promoter function in said *E. coli* cell.
36. The recombinant *E. coli* cell according to Claim 35, wherein said long chain
25 polyunsaturated fatty acid is docosahexenoic acid.
37. The recombinant *E. coli* cell according to Claim 35, wherein said nucleotide sequence is shown in a SEQ ID NO selected from the group consisting of SEQ ID NOS: 69, 71 and 76.
30
38. A plant oil produced by a recombinant plant cell wherein said plant oil comprises a long chain polyunsaturated fatty acid exogenous to said plant oil, wherein said plant cell is produced according to a method comprising:
transforming said plant cell or an ancestor of said plant cell with a vector comprising one
35 or more polypeptide of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid wherein each of said nucleic acids are operably linked to a promoter functional in said plant cell.

39. A plant oil according to Claim 38, wherein said long chain polyunsaturated fatty acid is eicosapentenoic acid.

- 5 40. A plant oil according to Claim 38, wherein said long chain polyunsaturated fatty acid is docosahexenoic acid.



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FIG. 1A

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EPA
productivity

pAA-NEB

AscI-AatII/NEB

+

pPA-NEB ($\Delta 2,3$)

PacI-AatII/NEB

Single ORF clones

ORF3 / pSTV 28

ORF 6 / pUC118

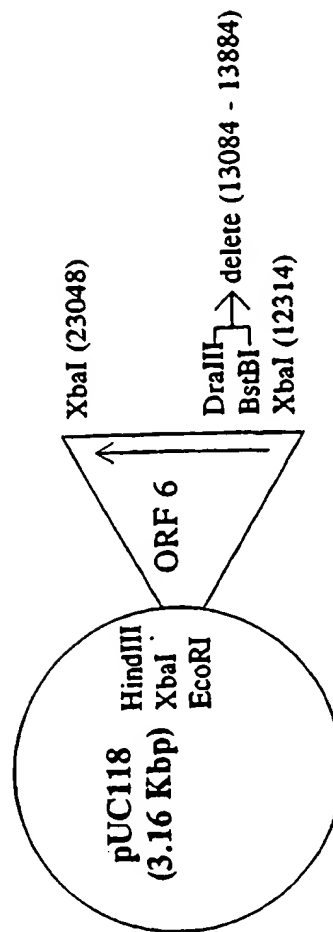
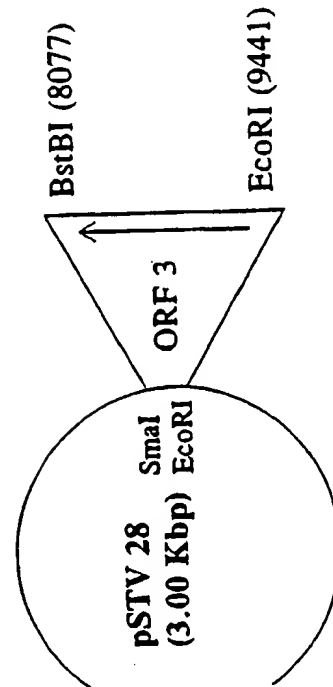


FIG. 1B

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Orf6 8.3 KB - 293 kD

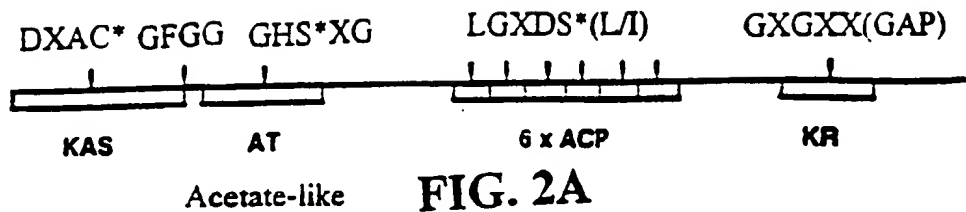


FIG. 2A

Orf7 2.3 KB - 84 kD

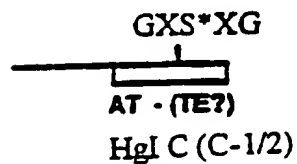


FIG. 2B

Orf3 0.8 KB - 30 kD



FIG. 2E

Orf8 6.0 KB - 217 kD

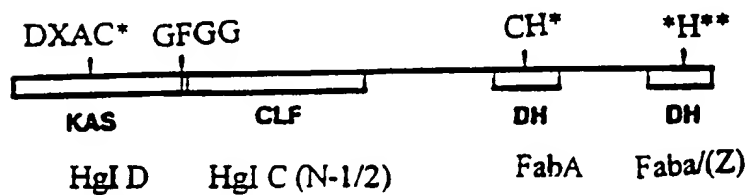


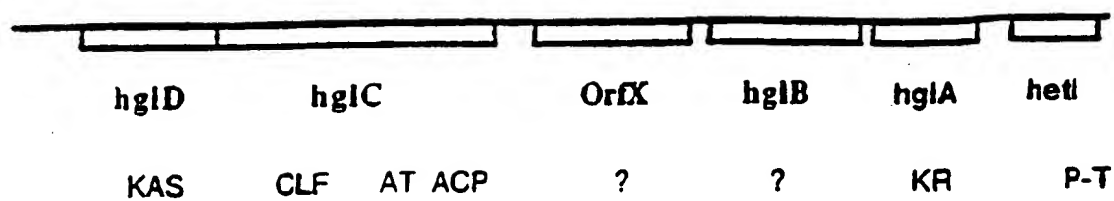
FIG. 2C

Orf9 1.6 KB - 59 kD

Anabeana - Orf552 homolog

FIG. 2D

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**FIG. 2F**

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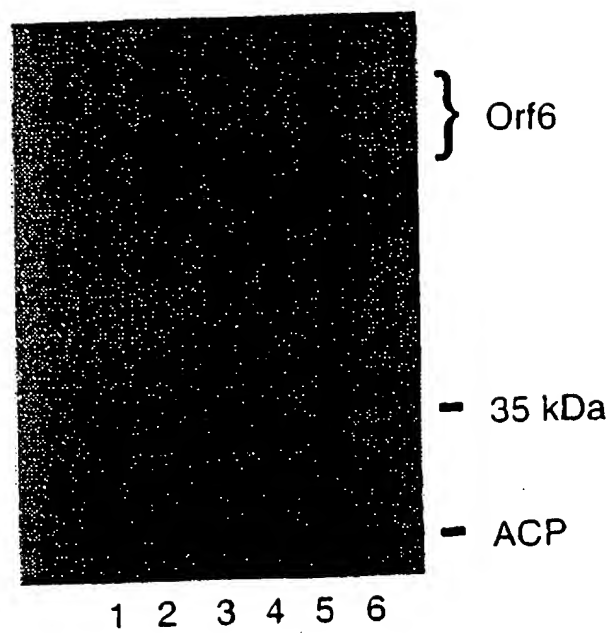


FIG. 3

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GATCTCTTAC AAAGAAACTA TCTCAATGTG AATTTAACCT TAATTCGGT TAATTACGGC 60
CTGATAGAGC ATCACCCCAAT CAGCCATAAA ACTGTAAAGT GGTACTCAA AGGTGGCTGG 120
GCGATTCTTC TCAAAATACAA AGTGCCCAAC CCAAGCAAAT CCATATCCGA TAACAGGTAA 180
AAGTAGCAAT AAACCCCGAGC GCTGAGTTAG TAATACATAA CGAATAATA GGATCACTAA 240
ACTACTGCCG AAATAGTGTA ATATTGACA GTTCTATGC TGATGTTGAG ATAAATAAAA 300
AGGGTAAAAAT TCAGCAAAAAG AACGATAGCG CTTACTCATT ACTCACACCT CGGTAAAAAA 360
GCAACTCGCC ATTAACTTGG CCAATCGTCA GTTGTTCTAT CGTCTCAAAG TTATGCCGAC 420
TAAATAAATC TATATGTGCA TTATGATTAG CAAAACTCC GATACCATCA AGATGAAAGT 480
GTTTCATCACA CCAACTCAAA ACTGCGTCGA TAAGCTTACT GCCATAGCCC TTGCCCTTGCT 540
CCACATTTCG GATAGCAATA AACTGTAAAA TGCCACATTG GCCACTTGGT AAGCTCTCTA 600
TAATCTGATT TTCTTTGTTA ATAAGTGCCT GAGTTGAATA CCAACCAGTA CTTAACAACA 660
TCCTTTAAACG CCAATGCCAA AAACGGCGCT CACCTAAGGG AACCTGCTGA GTCACATATGC 720
AGGCTACGCC TATCAATCTA TCCCCAACGA ACATACCAAT AAGTGCTTGC TCCTGTTGCC 780
AGAGCTCATT GAGTTCCTCT CGAATAGCCC CGCGAAGCTT TTGCTCATAC TGGCGTTGAT 840
CACCACATAA AAGTGTTTCG ATAAAAAAGG GATCATCATG ATAGGCGTTA TAGAGAATAG 900
AGGCTGCTAT GCGTAAATCT TCTGCCGCTG GATAAACTGC ACGACACTCT TCCATGGCTT 960
GATCTTCCAT TGTATTGTC CTTGACCTTG ATCACACAAC ACCAATGTAA CAAGACTGTA 1020

FIG. 4A-1

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TAGAAGTGCA ATTAATAATC AATTCGTGCA TTAAGCAGGT CAGCATTTCT TTGCTAAACA 1080
AGCTTTATTG GCTTTGACAA AACTTTGCCT AGACTTTAAC GATAGAAATC ATAATGAAAG 1140
AGAAAAGCTA CAACCTAGAG GGGAAATAATC AAACAACCTGC TAAGATCTAG ATAATGTAAT 1200
AAACACCGAG TTTATCGACC ATACTTAGAT AGAGTCATAG CAACGAGAAT AGTTATGGAT 1260
ACAAAGCCGC AAGATCTATC ACACCTGTTT TTACAGCTAG GATTAGCAA TGATCAACCC 1320
GCAATTGAAC AGTTTATCAA TGACCATCAA TTAGCGGACA ATATATTGCT ACATCAAGCA 1380
AGCTTTTGGA GCCCATCGCA AAAGCACTTC TTAATTGAGT CATTTAATGA AGATGCCCCAG 1440
TGGACCGAAG TCATCGACCA CTTAGACACC TTATTAAGAA AAAACTAACC ATTACAACAG 1500
CAACTTTAAA TTTTGCCGTA AGCCATCTCC CCCACCCCCA CAACAGCGTT GTTGCTTTATG 1560
ACCACTGGAG TACATTGTC TTTAGTCGTT TTACCATCAC CATGGGTACG TTGAGTGCGA 1620
TAAAAAAGCA CATAAACTTC TTTATCGGCC TGAATATAGG CTTCGTTAAA ATCAGCTGTT 1680
CCCATTAAAG TAACCACTTG CTCCTTACTC ATGCCCTAGAG ATATCTTTGT CAAATTGTCA 1740
CGGTTTTTAT CTTGAGTTTT CTCCTCAAGCA CCGTGATTAT CCCAGTCAGA TTCCCCCATCA 1800
CCAACATTGA CCACACAGCC CGTTAGCCCT AAGCTTGCAA TCCCAAAACA TGCTAAACCT 1860
AATAAATTTAT TTTTCATTTT AACTTCCTGT TATGACATTA TTTTTCCTTA GAAGAAAAGC 1920
AACTTACATG CCAAAACACA AGCTGTTGTT TTAATGACT TTATTTATTA TTAGCCCTTT 1980
AGGATATGCC TAGAGCAATA ATAATTACCA ATGTTTAAGG AATTGACTA ACTATGAGTC 2040

FIG. 4A-2

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CGATTGAGCA AGTGCTAACA GCTGCTAAAA AAATCAATGA ACAAGGTAGA GAACCAACAT 2100
TAGCATTGAT TAAAAACCAA CTTGGTAATA GCATCCCAAT GCGCGAGTTA ATCCAAGGTT 2160
TGCAACAGTT TAAGTCTATG AGTGCAGAAG AAAGACAAGC AATACCTAGC AGCTTAGCAA 2220
CAGCAAAAGA AACTCAATAT GGTCAATCAA GCTTATCTCA ATCTGAACAA GCTGATAGGA 2280
TCCTCCAGCT AGAAAAACGCC CTCAATGAAT TAAGAAAACGA ATTTAATGGG CTAAAAAGTC 2340
AATTGATAA CTTACAACAA AACCTGATGA ATAAAGAGCC TGACACCAAA TGCATGTAAT 2400
TGAACTACGA TTTGAATGTT TTGATAACAC CACGATTACT GCAGCAGAAA AAGCCATTAA 2460
TGGTTTGCTT GAAGCTTATC GAGCCAATGG CCAGGTTCTA GGTGCTGAAT TTGCCCGTTGC 2520
ATTTAACGAT GGTGAGTTTA AAGCACGCAT GTTAACCCCA GAAAAAAGCA GCTTATCTAA 2580
ACGCTTTAAT AGTCCTTGGG TAAATAGTGC ACTCGAAGAG CTAACCGAAG CCAAATTGCT 2640
TGCGCCACGT GAAAAGTATA TTGGCCAAGA TATTAATTCT GAAGCATCTA GCCAAGACAC 2700
ACCAAGTTGG CAGCTACTTT ACACAAAGTTA TGTGCACATG TGCTCACCAC TAAGAAATGG 2760
CGACACCTTG CAGCCTATTC CACTGTATCA AATTCCAGCA ACTGCCAAGC GCGATCATAA 2820
ACGAATGATC CGTTGGCAAA CAGAAATGGCA AGCTTGTGAT GAATTGCAAA TGGCCGCAGC 2880
TACTAAAGCT GAATTTGCCG CACTTGAAGA GCTAACCAGT CATCAGAGTG ATCTATTAG 2940
GCGTGGTTGG GACTTACGTG GCAGAGTCGA ATACTTGACG AAAATTCCGA CCTATTACTA 3000
TTTATACCGT GTTGGCGGTG AAAGCTTAGC AGTAGAAAAG CAGCGCTCTT GTCCTAAGTG 3060

FIG. 4A-3

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TGGCAGTCAA GAATGGCTGC TCGATAAACC ATTATTGGAT ATGTTCCATT TTGCTGTGA 3120
CACCTGCCGC ATCGTATCTA ATATCTCTTG GGACCATTTA TAACTCTTCC GAGTCTTATC 3180
ACACTAGAGT TTAGTCAGCA TAAAAATGGC GCTTATATTT CAATTAAAAG AAATATAAGC 3240
GCCATTTTCA TCGATACTAT ATATCAGCAG ACTATTTTCC GCGTAAATTA GCCCACATTA 3300
ATTTCAATTCT TTGCCAGATC CCTGGATGAT CTAGTTGTGG CATCGACTCT TCAATAGGTT 3360
TAACCGCAGG TGTAACCCCTT GGAGTCAATT CGTTTATAAA CTCGTTTAAA CTGTCACTTA 3420
ATTTAACGCT TTGTACTTCA CCTGGAATTT CAATCCATAC GTGCCATCA CTATTATTAA 3480
CCGTCAACAT TTTATCTTCA TCATCAAGAA TACCAATAAA CCAAGTCGGC TCTTGCTTAA 3540
GCTTTCCTTT CATCATTTAA TGACCAATGA TGTTTTGTG TAAGTATTCA AAATCAGTTT 3600
GATCCACAC TTGGATTAGC TCACCTTGGC CCCATTGTGA GTCAAAAAAT AGCGGTGCAG 3660
AAAAATGACT GCCAAAAAAT GGATTAATTT CTGCAGATAA TGTCATTTCAG AGTGCTGTTT 3720
CAACATTAGC AAATTCACCA GGTGTGTGAC GTACAACCGA TTGCCAAAAC ACTGCGCCAT 3780
CGGAGCCCGC TTCGGCGACA ACACACTCAG ACTTTGTGTC TTGCGCATAA TATCTTGGCT 3840
GTTCAACCAAG CTTATCCATG TAGGCTTGTT GATATTTAGA TAAAAAAGA TCTAAAGCAG 3900
GTAAAGAAGA CACTTAAGCC AGTTCCAAAA TCAGTTATAA TAGGGGTCTA TTTTGACATG 3960
GAAACCGTAT TGATGACACA ACATCATGAT CCCTACAGTA ACGCCCCCGA ACTTCTGAA 4020
TTAACTTTAG GAAAGTCGAC CGGTTATCAA GAGCAGTATG ATGCATCTTT ACTACAAGCG 4080

FIG. 4A-4

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TGCCGCGTAA ATTAAACCGT GATGCTATCG GTCTAACCAC TGAGCTACCT TTTCAATGGCT 4140
GTGATATTTG GACTGGCTAC GAACTGTCTT GGCTAAATGC TAAAGGCAAG CCAATGATTG' 4200
CTATTGCAGA CTTTAACCTA AGTTTGTATA GTAAAAATCT GATCGAGTCT AAGTCGTTTA 4260
AGCTGTATTT AAACAGCTAT AACCAAACAC GATTTGATAG CGTTCAAGCG GTTCAAGAAC 4320
GTTTAACTGA AGACTTAAGC GCCTGTGCCC AAGGCACAGT TACGGTAAAA GTGATTGAAC 4380
CTAAGCAATT TAACCACCTG AGAGTGGTTG ATATGCCAGG TACCTGCATT GACGATTTAG 4440
ATATTGAAGT TGATGACTAT AGCTTTAACT CTGACTATCT CACCGACAGT GTTGATGACA 4500
AAGTCATGGT TGCTGAAACG CTAACGTCAA ACTTATTGAA ATCAAACCTGC CTAATCACTT 4560
CTCAGCCTGA CTGGGGTACA GTGATGATCC GTTATCAAGG GCCTAAGATA GACCGTGAAA 4620
AGCTACTTAG ATATCTGATT TCATTTAGAC AGCACAAATGA ATTTCAATGAG CAGTGTGTTG 4680
AGCGTATATT TGTGTATTTA AAGCACTATT GCCAATGTGC CAAACTTACT GTCTATGCAC 4740
GTTATACCCG CCGTGGTGGT TTAGATATCA ACCCATATCG TAGCGACTTT GAAAACCCCTG 4800
CAGAAAAATCA GCGCCTAGCG AGACAGTAAT TGATTGCAGT ACCTACAAA AACCAATGCCT 4860
ATAAGCCCAAG CTTATGGGCA TTTTATATTT ATCAACTTGT CATCAAACTT CAGCCGCCAA 4920
GCCTTTTAGT TTTATCGCTA AATTAAAGCCG CTCTCTCAGC CAAATATTTG CAGGATTTTG 4980
CTGTAATTTA TGGCTCCACA CCATGAAATA CTCTATCGGC TCTACCGCAA AAGGTAAGTC 5040
AAATACCTGT AAGCCAAACA GCTTGGCATA TTCGTCAATG TGGGCTTTTG ACGCGATAGC 5100

FIG. 4A-5

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TAACGCATCA CTTTTTGAGG CAACCGACAT CATACTTAAT ATTGATGATT GCTCGCTGTG 5160
CATTTGCCCTT GCCGGTAACA CCTGTTTAGT CAGCAAGTCG GCAACACTTA AATTGTAGCG 5220
GCGCATCTTA AAAATAATAT GCTTTTCATT AAAGTATTGC TCTTGGCTCA ACCCACCTTG 5280
GATCCTTGGG TGAGCATTTT GTGCCACACA AACTAATTTA TCCTGCATTA CTTTTTGACT 5340
CTTAAATGCC GCAGATTCTG GCAGCCAAAT ATCTAAGGCT AAATCCACCT TTTCTAGTTG 5400
TAGGTCCATC TGCAACTCTT CTTCAATGAG CGGCGGCTCA CGAAATACAA TATTAATTGC 5460
AGTGCCCTGT AACACTTGCT CAATTGATC TTGCAAGAGT TGTATTGCCG ACTCGCTGGC 5520
ATACACATAA AAAGTTCGCT CACTTGAAGT GGGTCAAAAT GCTTCAAAAGC TAGTCGCAAC 5580
TTGCTCAATT GTTGACATAG CGCCCGCGAG CTGTTGATAA AGCGTCATCG CACTTGCGGT 5640
AGGTTTAACT CCCCTACCCA CTCGAGTAAA CAACTCTTCT CCAACAATAC TTTTGTAGCCT 5700
CGAAATCGCA TTACTAACCG ACGACTGAGT CAAATCCAGC TCTTCTGCCG CCCGGCTAAA 5760
AGATGAGGTG CGATACACCG CAGTAAAAAC GCGAAATAAA TTAAGATCAA AAGCTTTTG 5820
CTGCGACATA AATCAGCTAT CTCCTTATCC TTATCCTTAT CCTTATAAAA AGTTAGCTCC 5880
AGAGCACTCT AGCTCAAAA CAACTCAGCG TATTAAGCCA ATATTTTGGG AACTCAATTA 5940
ATATTCAATA TAAAAGTATT CATAATATAA ATACCAAGTC ATAATTTAGC CCTAATTATT 6000
AATCAATTCA AGTTACCTAT ACTGGCCTCA ATTAAGCAA TGTCTCATCA GTCTCCCTGC 6060
AACTAAATGC AATATTGAGA CATAAAGCTT TGAACGTATT CAATCTTACG AGGGTAACTT 6120

FIG. 4A-6

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ATGAAACAGA CTCTAATGGC TATCTCAATC ATGTGGCTTT TTTCAATCAA TGCCTAGCA 6180
GCGCAACATG AACATGACCA CATCACTGTT GATTACGAAG GGAAAGCCGC AACAGAACAC 6240
ACCATAGCTC ACAACCAAGC TGTAGCTAAA ACACCTTAACT TTGCCGACAC GCGTGCAATT 6300
GAGCAATCGT CTAATAATCT AGTCGCCAAG TTGATAAAG CAACTGCCGA TATATTACGT 6360
GCCGAATTG CTTTATTAG CGATGAAATC CCTGACTCGG TTAACCCGTC TCTCTACCGT 6420
CAGGCTCAGC TTAATATGGT GCCTAATGGT CTGTATAAAG TGAGCGATGG CATTTACCAG 6480
GTCCGCGGTA CCGACTTATC TAACCTTACA CTTATCCGCA GTGATAACGG TTGGATAGCA 6540
TAGGATGTTT TGTAAACCA AGAAGCAGCA AAAGCCCTCAC TACAATTGTC GTTAAAGAAT 6600
CTACCTAAAG ATGGCGATTT ACCCGTTGTT GCGATGATTT ACTCCCATAG CCATGCGGAC 6660
CACTTTGGCG GAGCTCGCGG TGTTCAAGAG ATGTTCCCTG ATGTCAAAGT CTACGGCTCA 6720
GATAACATCA CTAAAGAAAT TGTCGATGAG AACGTACTTG CCGGTAACGC CATGAGCCGC 6780
CGCGCAGCTT ATCAATACGG CGCAACACTG GGCAACACATG ACCACGGTAT TGTGTATGCT 6840
GCGCTAGGTA AAGGTCTATC AAAAGGTGAA ATCACTTACG TCGCCCCAGA CTACACCTTA 6900
AACAGTGAAG GCAAAATGGA AACGCTGACG ATTGATGGTC TAGAGATGGT GTTTATGGAT 6960
GCCTCGGGCA CCGAAGCTGA GTCAGAAATG ATCACTTATA TTCCCTCTAA AAAAGCGCTC 7020
TGGACGGCGG AGCTTACCTA TCAAGGTATG CACAACATTT ATACGCTGCG CGGCGCTAAA 7080
GTACGTGATG CGCTCAAGTG GTCAAAAGAT ATCAACGAAA TGATCAATGC CTTTGGTCAA 7140

FIG. 4A-7

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GATGTCGAAG TGCTGTTTGC CTCGCACTCT GCGCCAGTGT GGGGTAACCA AGCGATCAAC 7200
GATTTCTTAC GCCTACAGCG TGATAACTAC GGCCTAGTGC ACAATCAAAC CTTGAGACTT 7260
GCCAACGATG GTGTGGGTAT ACAAGATATT GCGGATGCGA TTCAAGACAC GATTCCAGAG 7320
TCTATCTACA AGACGTGGCA TACCAATGGT TACCACGGCA CTTATAGCCA TAACGCTAAA 7380
GCGGTTTATA ACAAATATCT AGGCTACTTC GATATGAACC CAGCCAACCT TAATCCGCTG 7440
CCAACCAAGC AAGAATCTGC CAAGTTTGTG GAATACATGG GCGGCGCAGA TGCCGCAATT 7500
AAGCGCGCTA AAGATGATTA CGCTCAAGGT GAATACCGCT TTGTTGCAAC GGCATTAAAT 7560
AAGGTGGTGA TGGCCGAGCC AGAAATGAC TCCGCTCGTC AATTGCTAGC CGATACCTAT 7620
GAGCAACTTG GTTATCAAGC AGAAGGGCT GCGTGGAGAA ACATTTACTT AACTGGCGCA 7680
CAAGAGCTAC GAGTAGGTAT TCAAGCTGGC GCGCCTAAAA CCGCATCGGC AGATGTCATC 7740
AGTGAATGG ACATGCCGAC TCTATTTGAC TTCTCGCGG TGAAGATTGA TAGTCAACAG 7800
GCGGCTAAGC ACGGCTTAGT TAAAGATGAAT GTTATCACCC CTGATACTAA AGATATTCTC 7860
TATATTGAGC TAAGCAACGG TAACTTAAGC AAGCAGTGG TCGACAAAGA GCAAGCAGCT 7920
GACGCAAACC TTATGGTTAA TAAAGCTGAC GTTAACCGCA TCTTACTTGG CCAAGTAACC 7980
CTAAAAGCGT TATTAGCCAG CGGCGATGCC AAGCTCACTG GTGATAAAAC GGCATTTAGT 8040
AAAATAGCCG ATAGCATGGT CGAGTTTACA CCTGACTTCG AAATCGTACC AACGCCCTGT 8100
AAATGAGGCA TTAATCTCAA CAAGTGCAAG CTAGACATAA AAATGGGCGG ATTAGACGCC 8160

FIG. 4A-8

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CCATTTTAA TGCAATTTTG AACTAGCTAG TCTTAGCTGA AGCTCGAACA ACAGCTTTAA 8220
AATTCACCTC TTCTGCTGCA ATACTTATTT GCTGACACTG ACCAATACTC AGTGCAAAAC 8280
GATAACTATC ATCAAGATGG CCCAGTAAAC AATGCCAATT ATCAGCAGCG TTCAATTTGCT 8340
GTTCTTTAGC CTCGAATCAA CCTAAACCAG ACTTTTGTGG CTCAGCCGTTA GGCTTATTAG 8400
AACTCGACTC TAGTAAAGCA AGACCAATAT CTGTGTTTAA CAAAACCTGT CGCTGATTAA 8460
GTTGATGCTC AACCTTGTGA TCCGCAATAG CATCGGAAAT ATCAACACAA TGGCTCAAGC 8520
TTTTAGGTGC ATTAACTCCA AGAAAAGTTT CGCTCAGTGC AGAGAAAGTCA AACGCAAAAG 8580
ATTTTAGCGA TAATGCCAGC CCAAGTCCTT TCGCTTTAAT GTAAGACTCC TTGAGCGCCC 8640
ACAAATCAA AAAAGCGGTCT CGCTGCAAGG CCTCTGGTAA CGCTAACAAAG GCTCGCTTTT 8700
CTGATTCAGA GAAATAATGA CTAAGAATAG AGTGGATATT GGTGCTGTTA CGGCAACGCT 8760
CAATGTCGAC GCCAAACTCA ATACTAGCAG AGTCAGTTTC CTCCTTGCTT GCCTGACTGG 8820
CGCCTTTATT ATCAGCAGTG CAAATGCCCTA CTAATAGCCA ATCTCCACTA TGAATCACAT 8880
TAAAGTGGAC CCCGGTTTGA GCAAATTGCG CATCACTCAA TCTAGGCTTA CCTTGTGCG 8940
CATATTCAA GGGCCATTCA TTGGGGCGTA TTTCACATAG TTGTGACAAAT AAAGCGCGCA 9000
AATAGCCTCT TACCATTAAA CCTTGAGTTT TAGCTTCTTG TTAAATGTAG CGATTAACT 9060
TAATTAACTC ATCTTCAGG AGCCATGACT TAACCAACTC TGTAGTCTGG TTATCGCACT 9120
CTTGATTTGT TAACGGACAG AAGTATAAGG AAATCAATCG AGAAGTTAGC AATTTTTCAG 9180

FIG. 4A-9

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GACACTCTTT AAAGCAACAA ACATAACCCC TATTTTACC AATTTAAGAT CAAAACTAAA 9240
GCCAAACTA ATTGAGAATA GTGTCAAACT AGCTTTAAAG GAAAAAATA TAAAAAGAAC 9300
ATTATACTTG TATAAATTAT TTTACACACC AAAGCCATGA TCTTCACAA ATTAGCTCCC 9360
TCTCCCTAAA ACAAGATTGA ATAAAAAAAT AAACCTTAAC TTTCATATAG ATAAAACAAA 9420
CCAATGGGAT AAAGTATATT GAATTCAATT TTAAGGAAAA ATTCAAATTG AATTCAGCT 9480
CTTCAGTAAA AGCATATTTT GCCGTTAGTG TGAAAAAATA CAAATTTAAA AACCAACATA 9540
GAACAAATA GCAGACAATA AAACCAAGGC GCAACACAAA CAACGCGCTT ACAATTTTCA 9600
CAAAAAAGCA ACAAGAGTAA CGTTTAGTAT TTGGATATGG TTATTGTAAT TGAGAATTTT 9660
ATAACAATTA TATTAAGGA ATGAGTATGT TTTTAAATC AAAACTTTTCG CGCTCAGTCA 9720
AACTTGCCAT ATCCGCAGGC TTAACAGCCT CGCTAGCTAT GCCTGTTTTT GCAGAAGAAA 9780
CTGCTGCTGA AGAACAAATA GAAAGAGTCG CAGTGACCGG ATCGCGAATC GCTAAAGCAG 9840
AGCTAACTCA ACCAGCTCCA GTCGTCAGCC TTTCAGCCGA AGAACTGACA AAATTTGGTA 9900
ATCAAGATTT AGGTAGCGTA CTAGCAGAAT TACCTGCTAT TGGTGCAACC AACACTATTA 9960
TTGGTAATAA CAATAGCAAC TCAAGCGCAG GTGTTAGCTC AGCAGACTTG CGTCGCTAG 10020
GTGCTAACAG AACCTTAGTA TTAGTCAACG GTAAGCGCTA CGTTGCCGC CAACCGGGCT 10080
CAGCTGAGGT AGATTTGTCA ACTATACCAA CTAGCATGAT CTCGCGAGTT GAGATTGTAA 10140
CCGGCGGTGC TTCAGCAATT TATGTTTCG ACGCTGTATC AGGTGTTATC AACGTTATCC 10200

FIG. 4A-10

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TTAAAGAAGA CTTTGAAGGC TTTGAGTTA ACGCAGTAC TAGCGTTCT ACTGAAAGTG 10260
TAGGCACTCA AGAGCACTCT TTTGACATTT TGGGTGGTGC AAACGTTGCA GATGGACGTG 10320
GTAATGTAAC CTTCTACGCA GGTATGAAC GTACAAAAGA AGTCATGGCT ACCGACATTC 10380
GCCAATTGCA TGCTTGGGGA ACAATTAAA ACGAAGCCGA TGGTGGTGAA GATGATGTA 10440
TTCCAGACAG ACTACGTGTA CCACGAGTTT ATTCTGAAAT GATTAATGCT ACCGGTGTTA 10500
TCAATGCATT TGGTGGTGA ATTGGTCGCT CAACCTTTGA CAGTAAACGGC AATCCTATTG 10560
CACAAACAAGA ACGTGATGGG ACTAACAGCT TTGCATTTGG TTCATTCCCT AATGGCTGTG 10620
ACACATGTTT CAACACTGAA GCATACGAAA ACTATATTCC AGGGGTAGAA AGAATAAACG 10680
TTGGCTCATC ATTCAACTTT GATTTTACCG ATAACATTCA ATTTTACACT GACTTCAGAT 10740
ATGTAAAGTC AGATATTCAG CAACAATTC AGCCTTCATT CCGTTTTGGT AACATTAATA 10800
TCAATGTTGA AGATAACGCC TTTTGTGAATG ACGACTTGCG TCAGCAAAATG CTCGATGCGG 10860
GTCAAACCAA TGCTAGTTT GCCAAGTTT TTGATGAATT AGGAAATCGC TCAGCAGAAA 10920
ATAAACGCGA ACTTTTCCGT TACGTAGGTG GCTTAAAGG TGGCTTTGAT ATTAGCGAAA 10980
CCATATTGA TTACGACCCT TACTATGTTT ATGGCGAGAC TAATAACCGT CGTAAACCC 11040
TTAATGACCT AATTCCCTGAT AACTTTGTG CAGCTGTGCA CTCTGTTATT GATCCTGATA 11100
CTGGCTTAGC AGCGTGTGCG TCACAAGTAG CAAGCGCTCA AGCGGATGAC TATACAGATC 11160
CCGCGTCTGT AAATGGTAGC GACTGTGTTG CTTATAACCC ATTGGCATG GGTCAGGCTT 11220

FIG. 4A-11

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CAGCAGAAGC CCGCGACTGG GTTCTGCTG ATGTGACTCG TGAAGACAAA ATAACTCAAC 11280
AAGTGATTGG TGGTACTCTC GGTACCGATT CTGAAGAACT ATTTGAGCTT CAAGGTGGTG 11340
CAATCGCTAT GGTGTGTTGGT TTTGAATACC GTGAAGAAAC GTCTGGTTCA ACAACCGATG 11400
AATTTACTAA AGCAGGTTTC TTGACAAGCG CTGCAACGCC AGATTCTTAT GGCGAATACG 11460
ACGTGACTGA GTATTTTGGT GAGGTGAACA TCCCAGTACT AAAAGAATTA CCTTTGCAC 11520
ATGAGTTGAG CTTTGACGGT GCATACCGTA ATGCTGATTA CTCACATGCC GGTAAGACTG 11580
AAGCATGGAA AGCTGGTATG TTCTACTCAC CATTAGAGCA ACTTGCATTA CGTGGTACGG 11640
TAGGTGAAGC AGTACGAGCA CCAACATTG CAGAAAGCCTT TAGTCCACGC TCTCCTGGTT 11700
TTGGCCGCCGT TTCAGATCCA TGTGATGCAG ATAACATTAA TGACGATCCG GATCGCGTGT 11760
CAAACGTGTC AGCATTGGGG ATCCCTCCAG GATTCCAAGC TAATGATAAC GTCAGTGTAG 11820
ATACCTTATC TGGTGGTAAC CCAGATCTAA AACCTGAAAC ATCAACATCC TTTACAGGTG 11880
GTCTTGTTG GACACCAACG TTTGCTGACA ATCTATCATT CACTGTCGAT TATTATGATA 11940
TTCAAATTGA GGATGCTATT TTGTCAGTAG CCACCCAGAC TGTGCTGAT AACTGTGTG 12000
ACTCAACTGG CGGACCTGAC ACCGACTTCT GTAGTCAAGT TGATCGTAAT CCAACGACCT 12060
ATGATATTGA ACTTGTTGCG TCTGGTTATC TAAATGCCG GCATTGAAT ACCAAAGGTA 12120
TTGAATTTCA AGCTGCATAC TCATTAGATC TAGAGTCTTT CAACGCGCCT GGTGAACACT 12180
GCTTCAACCT ATTGGGGAAC CAATTACTTG AACTAGAACG TCTTGAATTC CAAAATCGTC 12240

FIG. 4A-12

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CTGATGAGAT TAATGATGAA AAAGGCGAAG TAGGTGATCC AGAGCTGCAG TTCCGCCCTAG 12300
GCATCGATTA CCGTCTAGAT GATCTAAGTG TTAGCTGGAA CACGCGTTAT ATTGATAGCG 12360
TAGTAACTTA TGATGTCTCT GAAAATGGTG GCTCTCCTGA AGATTATAT CCAGGCCACA 12420
TAGGCTCAAT GACAACTCAT GACTTGAGCG CTACATACTA CATCAATGAG AACTTCATGA 12480
TTAACGGTGG TGTACGTAAC CTATTTGACG CACTTCCACC TGGATACACT AACGATGCGC 12540
TATATGATCT AGTTGGTCGC CGTGCATTCC TAGGTATTAA GGTAATGATG TAATTAATTA 12600
TTACGCCCTCT AACTAATAAA AATGCAATCT CTTCGTAGAG ATTGCATTTT TTTATGAAAT 12660
CCAATCTTAA ACTGGTTCTC CGAGCATCTT ACGCCTTAAA AACCCCGCCC CTCAATGTAA 12720
CGCCAAAGTT AATTGCTTAC ACGCACTTAC ACAACGAAAC AATTTCATTA ACACGAGACA 12780
CAGCTCACGC TTTTATTATT ACCCTTGATT TTA CTACATA AAATTGCGTT TTAGCGCACA 12840
AGTGTCTCC CAAGCTGGTC GTATCTGTAA TTATTCAGTC CCAGGTGATT GTATTGACCC 12900
ATAAGCTCAG GTAGTCTGCT CTGCCATTAG CTAAACAATA TTGACAAAAAT GCGGATAAAA 12960
TGTGGCTTAG CGCTAAGTTC ACCGTAAGTT TTATCGGCAT TAAGTCCCAA CAGATTATTA 13020
ACGGAAAACC GCTAAACTGA TGGCAAAAAT AAATAGTGAA CACTTGGATG AAGCTACTAT 13080
TACTTCGAAT AAGTGTAACG AACACAGAGAC TGAGGCTCGG CATAGAAATG CCACTACAAC 13140
ACCTGAGATG CGCCGATTCA TACAAGAGTC GGATCTCAGT GTTAGCCAAC TGTCTAAAAAT 13200
ATTAAATATC AGTGAAGCTA CCGTACGTAA GTGGCGCAAG CGTGACTCTG TCGAAAACTG 13260

FIG. 4A-13

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TCCTAATACC CCGCACCATC TCAATACCAC GCTAACCCCT TTGCAAGAAT ATGTGGTTGT 13320
GGGCCTGCGT TATCAATTGA AAATGCCATT AGACAGATTG CTCAAAGCAA CCCAAGAGTT 13380
TATCAATCCA AACGTGTCGC GCTCAGGTTT AGCAAGATGT TTGAAGCGTT ATGGCGTTTC 13440
ACGGGTGAGT GATATCCAAA GCCCACACGT ACCAATGCGC TACTTTAATC AAATTCCAGT 13500
CACTCAAGGC AGCGATGTGC AAACCTACAC CCTGCACCTAT GAAACGCTGG CAAAAACCTT 13560
AGCCTTACCT AGTACCGATG GTGACAATGT GGTGCAAGTG GTGTCTCTCA CCATTCCACC 13620
AAAGTTAACC GAAGAAGCAC CCAGTTCAAT TTTGCTCGGC ATTGATCCTC ATAGCGACTG 13680
GATCTATCTC GACATATACC AAGATGGCAA TACACAAGCC ACGAATAGAT ATATGGCTTA 13740
TGTGCTAAAA CACGGGCCAT TCCATTACG AAAGTTACTC GTGCGTAACT ATCACACCTT 13800
TTTACAGCGC TTTCCCTGGAG CGACGCAAAA TCGCCGCCCC TCTAAAGATA TGCCTGAAAC 13860
AATCAACAAG ACGCCTGAAA CACAGGCACC CAGTGGAGAC TCATAATGAG CCAGACCTCT 13920
AAACCTACAA ACTCAGCAAC TGAGCAAGCA CAAGACTCAC AAGCTGACTC TCGTTTAAAT 13980
AAACGACTAA AAGATATGCC AATTGCTATT GTTGGCATGG CGAGTATTTT TGCAAAACCTCT 14040
CGCTATTTGA ATAAGTTTTG GGACTTAATC AGCGAAAAAA TTGATGCGAT TACTGAATTA 14100
CCATCAACTC ACTGGCAGCC TGAAGAATAT TACGAGCGAG ATAAAAACCGC AGCAGACAAA 14160
AGCTACTGTA AACGTGGTGG CTTTTTGCCA GATGTAGACT TCAACCCCAAT GGAGTTTGGC 14220
CTGCCGCCAA ACATTTTGGG ACTGACCGAT TCATCGCAAC TATTATCACT CATCGTTGCT 14280

FIG. 4A-14

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AAAGAAGTGT TGGCTGATGC TAACTTACCT GAGAATTACG ACCGCGATAA AATTGGTATC 14340
ACCTTAGGTG TCGGCGGTGG TCAAAAAATT AGCCACAGCC TAACAGCGCG TCTGCAATAC 14400
CCAGTATTGA AGAAAGTATT CGCCAATAGC GGCATTAGTG ACACCGACAG CGAAATGCTT 14460
ATCAAGAAAT TCCAAGACCA ATATGTACAC TGGGAAGAAA ACTCGTTCCC AGGTTCACTT 14520
GGTAACGTTA TTGCGGGCCG TATCGCCAAC CGCTTCGATT TTGGCGGCAT GAACGTGTG 14580
GTTGATGCTG CCTGTGCTGG ATCACTTGCT GCTATGCCGA TGGCGCTAAC AGAGCTAACT 14640
GAAGGTCGCT CTGAAATGAT GATCACCGGT GGTGTGTGTA CTGATAACTC ACCCTCTATG 14700
TATATGAGCT TTTCAAAAAC GCCCGCCTTT ACCACTAACG AAACCATTTCA GCCATTTGAT 14760
ATCGACTCAA AAGGCATGAT GATTGGTGAA GGTATTGGCA TGGTGGCGCT AAAGCGTCTT 14820
GAAGATGCAG AGCGCGATGG CGACCGCATT TACTCTGTAA TTAAGAAGTGT GGGTGCATCA 14880
TCTGACGGTA AGTTTAAATC AATCTATGCC CCTCGGCCAT CAGGCCAAGC TAAAGCACTT 14940
AACCGTGCCT ATGATGACGC AGGTTTTCGG CCGCATACCT TAGGTCTAAT TGAAGCTCAC 15000
GGAACAGGTA CTGCAGCAGG TGACGCGGCA GAGTTTGCCG GCCTTTGCTC AGTATTGCT 15060
GAAGGCAACG ATACCAAGCA ACACATTGCG CTAGGTTTCAG TTAATCACA AATTGGTCAT 15120
ACTAAATCAA CTGCAGGTAC AGCAGGTTTA ATTAAAGCTG CTCTTGCTTT GCATCACAAAG 15180
GTACTGCCGC CGACCATTA CGTTAGTCAG CCAAGCCCTA AACTTGATAT CGAAAACTCA 15240
CCGTTTATC TAAACACTGA GACTCGTCCA TGGTTACCAC GTGTTGATGG TACGCCGCGC 15300

FIG. 4A-15

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CGCGGGGTA TTAGCTCATT TGGTTTGGT GGCACTAACT TCCATTTTGT ACTAGAAAGAG 15360
TACAACCAAG AACACAGCCG TACTGATAGC GAAAAAGCTA AGTATCGTCA ACGCCAAAGTG 15420
GCGCAAAGCT TCCTTGTTAG CGCAAGCGAT AAAGCATCGC TAATTAAACGA GTTAAACGTA 15480
CTAGCAGCAT CTGCAAGCCA AGCTGAGTTT ATCCTCAAAG ATGCAGCAGC AAACATATGGC 15540
GTACGTGAGC TTGATAAAAA TGCACCACGG ATCGGTTTAG TTGCAAAACAC AGCTGAAGAG 15600
TTAGCAGGCC TAATTAAAGCA AGCACTTGCC AAAC TAGCAG CTAGCGATGA TAACGCATGG 15660
CAGCTACCTG GTGGCACTAG CTACCGCGCC GCTGCAGTAG AAGTAAAGT TGCCGCACTG 15720
TTTGCTGGCC AAGGTTTACA ATATCTCAAT ATGGGCCGTG ACCTTACTTG TTATTACCCA 15780
GAGATGCGTC AGCAATTTGT AACTGCAGAT AAAGTATTTG CCGCAAAATGA TAAACGCGG 15840
TTATCGCAAA CTCTGTATCC AAAGCCTGTA TTTAATAAAG ATGAATTAAA GGCTCAAGAA 15900
GCCATTTTGA CCAATACCGC CAATGCCCAA AGCGGAATTG GTGCGATTTC AATGGGTCAA 15960
TACGATTTGT TTAGTGCGGC TGGCTTTAAT GCCGACATGG TTGCAGGCCA TAGCTTTGGT 16020
GAGCTAAGTG CACTGTGTGC TGCAGGTGTT ATTTCAGCTG ATGACTACTA CAAGCTGGCT 16080
TTTGCTCGTG GTGAGGCTAT GGCAACAAAA GCACCGGCTA AAGACGGCGT TGAAGCAGAT 16140
GCAGGAGCAA TGTTTGCAAT CATAACCAAG AGTGCTGCAG ACCTTGAAAC CGTTGAAGCC 16200
ACCATCGCTA AATTGTATGG GGTGAAAGTC GCTAACTATA ACGCGCCAAAC GCAATCAGTA 16260
ATTGCAGGCC CAACAGCAAC TACCGCTGAT GCGGCTAAAG CGCTAACTGA GCTTGGTTAC 16320

FIG. 4A-16

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AAAGCGATTA ACCTGCCAGT ATCAGGTGCA TTCCAACA CTG AACTTGTGG TCACGCTCAA 16380
GGCCCATTTG CTAAAGCGAT TGACGCAGCC AAATTACTA AAACAAGCCG AGCACTTTAC' 16440
TCAAATGCAA CTGGCGGACT TTATGAAAGC ACTGCTGCAA AGATTAAAGC CTCGTTTAAG 16500
AAACATATGC TTCAATCAGT GCGCTTTACT AGCCAGCTAG AAGCCATGTA CAACGACGGC 16560
GCCCGTGTAT TTGTTGAATT TGGTCCAAAG AACATCTTAC AAAAATTAGT TCAAGGCACG 16620
CTTGTCACAA CTGAAATGA AGTTTGCACT ATCTCTATCA ACCCTAATCC TAAAGTTGAT 16680
AGTGATCTGC AGCTTAAAGCA AGCAGCAATG CAGCTAGCGG TTACTGGTGT GGTA CTGAT 16740
GAAATTGACC CATAACCAAGC CGATATTGCC GCACCAGCGA AAAAGTCGCC AATGAGCAT 16800
TCGCTTAATG CTGCTAACCA TATCAGCAAA GCAACTCGCG CTAAGATGGC CAAGTCCTTA 16860
GAGACAGGTA TCGTCACCTC GCAAAATAGAA CATGTTATTG AAGAAAAAAT CGTTGAAGTT 16920
GAGAAACTGG TTGAAAGTCGA AAAGATCGTC GAAAAAGTGG TTGAAGTAGA GAAAGTTGTT 16980
GAGGTTGAAG CTCCTGTTAA TTCAGTGCAA GCCAATGCAA TTCAAACCCG TTCAGTTGTC 17040
GCTCCAGTAA TAGAGAACCA AGTCGTGTCT AAAAACAGTA AGCCAGCAGT CCAGAGCAT 17100
AGTGGTGATG CACTCAGCAA CTTTTTTGCT GCACAGCAGC AAACCGCACA GTTGCA TCAG 17160
CAGTTCTTAG CTATTCCGCA GCAATATGGT GAGACGTTCA CTACGCTGAT GACCGAGCAA 17220
GCTAAACTGG CAAGTTCTGG TGTGCAATT CCAGAGAGTC TGCAACGCTC AATGGAGCAA 17280
TTCCACCAAC TACAAGCGCA AACACTACAA AGCCACACCC AGTTCCTTGA GATGCAAGCG 17340

FIG. 4A-17

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GGTAGCAACA TTGCAGCGTT AACCTACTC AATAGCAGCC AAGCAACTTA CGCTCCAGCC 17400
ATTCACAATG AAGCGATTCA AAGCCAAAGTG GTTCAAAGCC AAAGTGCAGT CCAGCCAGTA 17460
ATTTCAACAC AAGTTAACCA TGTGTCAGAG CAGCCAACTC AAGCTCCAGC TCCAAAAGCG 17520
CAGCCAGCAC CTGTGACAAC TGCAGTTCAA ACTGCTCCGG CACAAGTTGT TCGTCAAGCC 17580
GCACCAGTTC AAGCCGCTAT TGAACCGATT AATACAAAGTG TTGCGACTAC AACGCCTTCA 17640
GCCTTCAGCG CCGAAACAGC CCTGAGCGCA ACAAAGTCC AAGCCACTAT GCTTGAAAGTG 17700
GTTGCTGAGA AAACCGGTTA CCCAACTGAA ATGCTAGAGC TTGAAAATGGA TATGGAAAGCC 17760
GATTTAGGCA TCGATTCTAT CAAGCGTGTA GAAATTCTTG GCACAGTACA AGATGAGCTA 17820
CCGGGTCTAC CTGAGCTTAG CCTGAAGAT CTAGCTGAGT GTCGAACGCT AGGCGAAATC 17880
GTTGACTATA TGGGCAGTAA ACTGCCGGCT GAAGGCTCTA TGAATTCTCA GCTGTCTACA 17940
GGTTCCGCAG CTGCGACTCC TGCAGCGAAT GGTCTTTCTG CGGAGAAAGT TCAAGCGACT 18000
ATGATGTCTG TGGTTGCCGA AAAGACTGGC TACCCCAACTG AAATGCTAGA GCTTGAAATG 18060
GATATGGAAG CCGATTTAGG CATAGATTCT ATCAAGCGCG TTGAAATTCT TGGCACAGTA 18120
CAAGATGAGC TACCGGGTCT ACCTGAGCTT AGCCCTGAAG ATCTAGCTGA GTGTCGTACT 18180
CTAGGCGAAA TCGTTGACTA TATGAACTCT AAAGTCCGCTG ACGGCTCTAA GCTGCCGGCT 18240
GAAGGCTCTA TGAATTCTCA GCTGTCTACA AGTGCCGCAG CTGCGACTCC TGCAGCGAAT 18300
GGTCTCTCTG CGGAGAAAGT TCAAGCGACT ATGATGTCTG TGGTTGCCGA AAAGACTGGC 18360

FIG. 4A-18

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TACCCAACTG AAATGCTAGA ACTTGAAATG GATATGGAAG CTGACCTTGG CATCGATTCA 18420
ATCAAGCGCG TTGAAATTTCT TGGCACAGTA CAAGATGAGC TACCGGGTTT ACCTGAGCTA' 18480
AATCCAGAAG ATTTGGCAGA GTGTCGTACT CTTGGCGAAA TCGTGACTTA TATGAACTCT 18540
AAACTCGCTG ACGGCTCTAA GCTGCCAGCT GAAGGCTCTA TGCACTATCA GCTGTCTACA 18600
AGTACCGCTG CTGCGACTCC TGTAGCGAAT GGTCCTCTCTG CAGAAAAAGT TCAAGCGACC 18660
ATGATGCTG TAGTTGCAGA TAAAACTGGC TACCCAACTG AAATGCTTGA ACTTGAAATG 18720
GATATGGAAG CCGATTTAGG TATCGATTCT ATCAAGCGCG TTGAAATTCT TGGCACAGTA 18780
CAAGATGAGC TACCGGGTTT ACCTGAGCTA AATCCAGAAG ATCTAGCAGA GTGTGCGACC 18840
CTAGGCGAAA TCGTTGACTA TATGGGCAGT AAATGCGCG CTGAAGGCTC TGCTAATACA 18900
AGTGCCGCTG CGTCTCTTAA TGTTAGTCC GTTGCGGCGC CTCGAAGCTGC TGCGACTCCT 18960
GTATCGAACG GTCTCTCTGC AGAGAAAAGTG CAAAGGACTA TGATGTCAGT AGTTGCAGAA 19020
AAGACCGGCT ACCCRAACTGA AATGCTAGAA CTTGGCATGG ATATGGAAGC CGATTTAGGT 19080
ATCGACTCAA TTAAACGCGT TGAGATTCTT GGCACAGTAC AAGATGAGCT ACCGGGTCTA 19140
CCAGAGCTTA ATCCTGAAGA TTTAGCTGAG TGCCGTACGC TGGGCGAAAT CGTTGACTAT 19200
ATGAACTCTA AGCTGGCTGA CGGCTCTAAG CTTCCAGCTG AAGGCTCTGC TAATACAAGT 19260
GCCACTGCTG CGACTCCTGC AGTGAATGGT CTTTCTGCTG ACAAGGTACA GCGGACTATG 19320
ATGTCTGTAG TTGCTGAAAA GACCGGCTAC CCAACTGAAA TGCTAGAACT TGGCATGGAT 19380

FIG. 4A-19

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ATGGAAGCAG ACCTTGGTAT TGATTCTATT AAGCGCGTTG AAATTCTTGG CACAGTACAA 19440
GATGAGCTCC CAGGTTTACC TGAGCTTAAT CCTGAAGATC TCGCTGAGTG CCGCACGCTT 19500
GGCGAAATCG TTAGCTATAT GAACTCTCAA CTGGCTGATG GCTCTAAACT TTCTACAAAGT 19560
GCGGCTGAAG GCTCTGCTGA TACAAAGTGCT GCAAATGCTG CAAAGCCGGC AGCAATTTTCG 19620
GCAGAACCAA GTGTTGAGCT TCCTCCTCAT AGCGAGGTAG CGCTAAAAAA GCTTAATGCG 19680
GCGAACCAAGC TAGAAAAATTG TTTCGCCGCA GACGCAAGTG TTGTGATTAA CGATGATGGT 19740
CACAAACGCAG GCGTTTTAGC TGAGAAAACTT ATTAAACAAG GCCTAAAAAGT AGCCGTTGTG 19800
CGTTTACCGA AAGGTCAGCC TCAATCGCCA CTTTCAAGCG ATGTTGCTAG CTTTGAGCTT 19860
GCCTCAAGCC AAGAACTCTGA GCTTGAAAGCC AGTATCACTG CAGTTATCGC GCAGATTGAA 19920
ACTCAGGTTG GCGCTATTGG TGGCTTTATT CACTTGCAAC CAGAAAGCGAA TACAGAAAGAG 19980
CAAACGGCAG TAAACCTAGA TCGGCAAAAGT TTTACTCAGC TTAGCAATGC GTTCTTGTGG 20040
GCCAAATTAT TGCAACCCAAA GCTCGTTGCT GGAGCAGATG CGCGTCGCTG TTTTGTAAACA 20100
GTAAAGCCGTA TCGACGGTGG CTTTGGTTAC CTAAATACTG ACGCCCTAAA AGATGCTGAG 20160
CTAAACCAAAG CAGCATTAGC TGGTTTAACT AAAACCTTAA GCCATGAATG GCCACAAAGTG 20220
TTCTGTGCGG CGCTAGATAT TGCAACAGAT GTTGATGCAA CCCATCTTGC TGATGCAATC 20280
ACCAGTGAAC TATTTGATAG CCAAGCTCAG CTACCTGAAG TGGGCTTAAG CTTAATTGAT 20340
GGCAAAAGTTA ACCGCGTAAC TCTAGTTGCT GCTGAAGCTG CAGATAAAAC AGCAAAAGCA 20400

FIG. 4A-20

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GAGCTTAACA GCACAGATAA AATCTTAGTG ACTGGTGGGG CAAAAGGGGT GACATTTGAA 20460
TGTGCACTGG CATTAGCATC TCGCAGCCAG TCTCACTTTA TCTTAGCTGG GCGCAGTGAA 20520
TTACAAGCTT TACCAAGCTG GGCTGAGGGT AAGCAAACTA GCGAGCTAAA ATCAGCTGCA 20580
ATCGCACATA TTATTTCTAC TGGTCAAAAG CCAACGCCTA AGCAAGTTGA AGCCGCTGTG 20640
TGGCCAGTGC AAAGCAGCAT TGAATAAT GCGGCCCTAG CCGCCTTTAA CAAAGTTGGC 20700
GCCTCAGCTG AATACGTCAG CATGGATGTT ACCGATAGCG CCGCAATCAC AGCAGCACTT 20760
AATGGTCGCT CAAATGAGAT CACCGGTCTT ATTCAATGGC CAGGTGTACT AGCCGACAAG 20820
CATATTCAAG ACAAGACTCT TGCTGAACTT GCTAAAGTTT ATGGCACTAA AGTCAACGGC 20880
CTAAAAGCGC TGCTCGCGGC ACTTGAGCCA AGCAAAATTA AATTACTTGC TATGTTTCTCA 20940
TCTGCAGCAG GTTTTTACGG TAATATCGGC CAAAGCGATT ACGCGATGTC GAACGATATT 21000
CTTAACAAGG CAGCGCTGCA GTTCACCGCT CGCAACCCAC AAGCTAAAAGT CATGAGCTTT 21060
AACTGGGGTC CTTGGGATGG CGGCATGGTT AACCCAGCGC TTAAAAAGAT GTTACCCGAG 21120
CGTGGTGTGT ACGTTATTCC ACTAAAAGCA GGTGCAGAGC TATTTGCCAC TCAGCTATTG 21180
GCTGAACCTG GCGTGCAGTT GCTCATTTGGT ACGTCAATGC AAGGTGGCAG CGACACTAAA 21240
GCAACTGAGA CTGCTTCTGT AAAAAAGCTT AATCGGGTG AGGTGCTAAG TGCATCGCAT 21300
CCGCGTGTGT GTGCACAAAA AACACCACTA CAAGCTGTCA CTGCAACGCG TCTGTTAACC 21360
CCAAGTGCCA TGGTCTTTCAT TGAAGATCAC CGCATTTGGC GTAACAGTGT GTTGCCAACG 21420

FIG. 4A-21

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GTATGCGCCA TCGACTGGAT GCGTGAAGCG GCAAGCGACA TGCTTGGCGC TCAAGTTAAG 21480
GTAAGTTGATT ACAAGCTATT AAAAGGCATT GTATTTGAGA CTGATGAGCC GCAAGAGTTA 21540
ACACTTGAGC TAACGCCAGA CGATTACAGC GAAGCTACGC TACAAGCATT AATCAGCTGT 21600
AATGGGCGTC CGCAATACAA GCGACGCTT ATCAGTGATA ATGCCGATAT TAAGCAACTT 21660
AACAAGCAGT TTGATTTAAG CGCTAAGCG ATTACCACAG CAAAAGAGCT TTATAGCAAC 21720
GGCACCTTGT TCCACGGTCC GCGTCTACAA GGGATCCCAAT CTGTAGTGCA GTTCGATGAT 21780
CAAGGCTTAA TTGCTAAAAGT CGCTCTGCCT AAGGTTGAAC TTAGCGATTG TGGTGAGTTC 21840
TTGCGCGCAA CCCACATGGG TGGCAGTCAA CCTTTTGCTG AGGACTTGCT ATTACAAGCT 21900
ATGCTGGTTT GGGCTCGCCT TAAACTGGC TCGGCAAGTT TGCCATCAAG CATTGGTGAG 21960
TTTACCTCAT ACCAACCCTT GGCCTTTGGT GAAACTGGTA CCATAGAGCT TGAAGTGATT 22020
AAGCACAACA AACGCTCACT TGAAGCGAAT GTTGCCTAT ATCGTGACAA CGGCGAGTTA 22080
AGTGCCATGT TTAAGTCAGC TAAATCACC ATTAGCAAAA GCTTAAATTC AGCATTTTAA 22140
CCTGCTGTCT TAGCAAAACGA CAGTGAGGCG AATTAGTGA ACAAACGCCT AAAGCTAGTG 22200
CGATGCCGCT GCGCATCGCA CTTATCTTAC TGCCAACACC GCAGTTTGAA GTTAACTCTG 22260
TCGACCAGTC AGTATTAGCC AGCTATCATA CACTGCAGCC TGAGCTAAAT GCCCTGCTTA 22320
ATAGTGCGCC GACACCTGAA ATGCTCAGCA TCACTATCTC AGATGATAGC GATGCAACA 22380
GCTTTGAGTC GCAGCTAAAT GCTGCGACCA ACGCAATTAA CAATGGCTAT ATCGTCAAGC 22440

FIG. 4A-22

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TTGCTACGGC AACTCACGCT TTGTTAATGC TGECTGCATT AAAAGCGGCG CAAATGCGGA 22500
TCCATCCTCA TCGCGAGCTT GCCGCTATGC AGCAAGCTAA ATCGACGCCA ATGAGTCAAG 22560
TATCTGGTGA GCTAAAGCTT GCGGCTAATG CGCTAAGCCT AGCTCAGACT AATGCGCTGT 22620
CTCATGCTTT AAGCCAAAGCC AAGCGTAACT TAACTGATGT CAGCGTGAAT GAGTGTTTTG 22680
AGAACCTCAA AAGTGAACAG CAGTTCACAG AGGTTTATTC GCTTATTCAG CAACTTGCTA 22740
GCCGCACCCA TGTGAGAAA GAGGTTAATC AAGGTGTGA ACTTGGCCCT AAACAAGCCA 22800
AAAGCCACTA TTGGTTTAGC GAATTCACC AAAACCGTGT TGCTGCCATC AACTTTATTA 22860
ATGGCCCAACA AGCAACCAGC TATGTGCTTA CTCAAGGTTT AGGATTGTTA GCTGCGAAAT 22920
CAATGCTAAA CCAGCAAAGA TTAATGTTTA TCTTGCCGGG TAACAGTCAG CAACAAATAA 22980
CCGCATCAAT AACTCAGTTA ATGCAGCAAT TAGAGCGTTT GCAGGTAACT GAGGTTAATG 23040
AGCTTTCTCT AGAATGCCAA CTAGAGCTGC TCAGGATAAT GTATGACAAC TTAGTCAACG 23100
CAGACAAACT CACTACTCGC GATAGTAAGC CCGCTTATCA GGCTGTGATT CAAGCAAGCT 23160
CTGTTAGCGC TGCAAAGCAA GAGTTAAGCG CGCTTAACGA TGCACTCACA GCGCTGTTTG 23220
CTGAGCAAAC AAACGCCACA TCAACGAATA AAGGCTTAAT CCAATACAAA ACACCGGCGG 23280
GCAGTTACTT AACCCTAACA CCGCTTGGA GCAACAATGA CAACGCCCAA GCGGCTCTTG 23340
CTTTTGCTA TCCGGGTGTG GGAACGGTTT ACGCCGATAT GCTTAATGAG CTGCATCAGT 23400
ACTTCCCTGC GCTTTACGCC AAACCTGAGC GTGAAGGCGA TTTAAAGGCG ATGCTACAAG 23460

FIG. 4A-23

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CAGAAGATAT CTATCATCTT GACCCTAAAC ATGCTGCCCA AATGAGCTTA GGTGACTTAG 23520
CCATTGCTGG CGTGGGAGC AGCTACCTGT TAACTCAGCT GCTCACCGAT GAGTTTAATA 23580
TTAAGCCTAA TTTTGCATTA GGTACTCAA TGGGTGAAGC ATCAATGTGG GCAAGCTTAG 23640
GCGTATGGCA AAACCCGCAT GCGCTGATCA GCAAAACCCA AACCGACCCG CTATTACTT 23700
CTGCTATTTC CGGCAAAATTG ACCGCGGTTA GACAAGCTTG GCAGCTTGAT GATACCGCAG 23760
CGGAAATCCA GTGGAATAGC TTTGTGGTTA GAAGTGAAGC AGCGCCGATT GAAAGCCTTGC 23820
TAAAGATTA CCCACACGCT TACCTGCGA TTATTCAAGG GGATACCTGC GTAATCGCTG 23880
GCTGTGAAAT CCAATGTAAA GCGCTACTTG CAGCACTGGG TAAACGCGGT ATTGCAGCTA 23940
ATCGTGTAAAC GCGGATGCAT ACGCAGCCTG CGATGCAAGA GCATCAAAAT GTGATGGATT 24000
TTTATCTGCA ACCGTTAAAA GCAGAGCTTC CTAGTGAAAT AAGCTTTATC AGCGCCGCTG 24060
ATTTAACTGC CAAGCAAACG GTGAGTGAGC AAGCACTTAG CAGCCAAGTC GTTGCTCAGT 24120
CTATTGCCGA CACCTTCTGC CAAACCTTGG ACTTTACCGC GCTAGTACAT CACGCCCAAC 24180
ATCAAGGCGC TAAGCTGTTT GTTGAAAATTG GCGCGGATAG ACAAAACTGC ACCTTGATAG 24240
ACAAGATTGT TAAACAAGAT GGTGCCAGCA GTGTACAACA TCAACCTTGT TGCACAGTGC 24300
CTATGAACGC AAAAGGTAGC CAAGATATTA CCAGCGTGAT TAAAGCGCTT GGCCAATTAA 24360
TTAGCCATCA GGTGCCATTA TCGGTGCAAC CATTATTGA TGGACTCAAG CGCGAGCTAA 24420
CACTTTGCCA ATTGACCAGC CAACAGCTGG CAGCACATGC AAATGTTGAC AGCAAGTTTG 24480

FIG. 4A-24

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AGTCTAACCA AGACCATTTA CTTCAAGGGG AAGTCTAATG TCATTACCAG ACAATGCTTC 24540
TAACCACCTT TCTGCCAACC AGAAAGGGCG ATCTCAGGCA AGTAAAAACCA GTAAGCAAAG' 24600
CAAAATCGCC ATTGTCGGTT TAGCCACTCT GTATCCAGAC GCTAAAAACCC CGCAAGAATT 24660
TTGGCAGAAAT TTGCTGGATA AACGGGACTC TCGCAGCACC TTAACATAACG AAAAACTCGG 24720
CGCTAACAGC CAAGATTATC AAGGTGTGCA AGGCCAATCT GACCGTTTTT ATTGTAATAA 24780
AGGCGGCTAC ATTGAGAACT TCAGCTTTAA TGCTGCAGGC TACAAATTGC CGGAGCAAAG 24840
CTTAAATGGC TTGGACGACA GCTTCCTTTG GGGGCTCGAT ACTAGCCGTA ACGCACTAAT 24900
TGATGCTGGT ATTGATATCA ACGGGCGCTGA TTTAAGCCGC GCAGGTGTAG TCATGGGCGC 24960
GCTGTCGTTT CCAACTFACCC GCTCAAAACGA TCTGTTTTTTG CCAATTTATC ACAGCGCCGT 25020
TGAAAAAGCC CTGCAAGATA AACTAGGCGT AAAGGCATTT AAGCTAAGCC CAACTAATGC 25080
TCATAACCGT CGCGCGGCAA ATGAGAGCAG CCTAAATGCA GCCAATGGTG CCATTGCCCC 25140
TAACAGCTCA AAAGTGGTGG CCGATGCACT TGGCCTTGGC GGCACACAAC TAAGCCTAGA 25200
TGCTGCCTGT GCTAGTTCGG TTTACTCATT AAAGCTTGCC TGGGATTACC TAAGCACTGG 25260
CAAAAGCCGAT ATCATGCTAG CAGGCGCAGT ATCTGGCGCG GATCCTTTCT TTATTAAATAT 25320
GGGATTCTCA ATCTTCCACG CCTACCCAGA CCATGGTATC TCAGTACCGT TTGATGCCAG 25380
CAGTAAAGGT TTGTTTGCTG GCGAAGGCG TGGCGTATTA GTGCTTAAAC GTCTTGAAGA 25440
TGCCGAGCGC GACAATGACA AAATCTATGC GGTGTTAGC GCGTAGGTC TATCAAAACGA 25500

FIG. 4A-25

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CGGTAAAGGC CAGTTTGTAT TAAGCCCCTAA TCCAAAAGGT CAGGTGAAGG CCTTTGAACG 25560
TGCTTATGCT GCCAGTGACA TTGAGCCCAA AGACATTGAA GTGATTGAGT GCCACGCAAC 25620
AGGCACACCG CTTGGCGGATA AAATTGAGCT CACTTCAATG GAAACCTTCT TTGAAGACAA 25680
GCTGCAAGGC ACCGATGCAC CGTTAATTGG CTCAGCTAAG TCTAACTTAG GCCACCTATT 25740
AACTGCAGCG CATGCGGGGA TCATGAAGAT GATCTTCGCC ATGAAAAGAG GTTACCTGCC 25800
GCCAAGTATC AATATTAGTG ATGCTATCGC TTCGCCGAAA AACTCTTCG GTAAACCAAC 25860
CCTGCCCTAGC ATGGTTCAAG GCTGGCCAGA TAAGCCATCG AATAATCATT TTGGTGTAAG 25920
AACCCGTCAC GCAGGCGTAT CGGTATTGG CTTTGGTGGC TGTAACGCCC ATCTGTTGCT 25980
TGAGTCATAC AACGGCAAAG GAACAGTAAA GGCAGAAGCC ACTCAAGTAC CGCGTCAAGC 26040
TGAGCCGCTA AAAGTGGTTG GCCTTGCCTC GCACTTTGGG CCTCTTAGCA GCATTAATGC 26100
ACTCAACAAT GCTGTGACCC AAGATGGGAA TGGCTTTATC GAACTGCCGA AAAAGCGCTG 26160
GAAAGGCCTT GAAAAGCACA GTGAACTGTT AGCTGAATTT GGCTTAGCAT CTGCGCCAAA 26220
AGGTGCTTAT GTGATAACT TCGAGCTGGA CTTTTTACGC TTTAAACTGC CGCCAAACGA 26280
AGATGACCGT TTGATCTCAC AGCAGCTAAT GCTAATGCCA GTAACAGACG AAGCCATTCTG 26340
TGATGCCAAG CTTGAGCCGG GGCAAAAAGT AGCTGTATTA GTGGCAATGG AAACCTGAGCT 26400
TGAACGTGAT CAGTTCCGGG GCCGGGTTAA CTTGCATACT CAATTAGCGC AAAGTCTTGC 26460
CGCCATGGGC GTGAGTTTAT CAACGGATGA ATACCAAGCG CTTGAAGCCA TCGCCATGGÀ 26520

FIG. 4A-26

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CAGCGTGCTT GATGCTGCCA AGCTCAATCA GTACACCAGC TTTATTGGTA ATATTATGGC 26580
GTCACGCGTG GCGTCACTAT GGGACTTTAA TGGCCCAGCC TTCACTATTT CAGCAGCAGA' 26640
GCAATCTGTG AGCCGCTGTA TCGATGTGGC GCAAAACCTC ATCATGGAGG ATAACCTAGA 26700
TGCGGTGGTG ATTGCAGCGG TCGATCTCTC TGGTAGCTTT GAGCAAGTCA TTCTTAAAAA 26760
TGCCATTGCA CCTGTAGCCA TTGAGCCAAA CCTCGAAGCA AGCCTTAATC CAACATCAGC 26820
AAGCTGGAAT GTCGGTGAAG GTGCTGGCGC GGTCGTGCTT GTTAAAAATG AAGCTACATC 26880
GGGCTGCTCA TACGGCCAAA TTGATGCACT TGGCTTTGCT AAAACTGCCG AAACAGCGTT 26940
GGCTACCGAC AAGCTACTGA GCCAAACTGC CACAGACTTT AATAAGGTTA AAGTGATTGA 27000
AACTATGGCA GGCCTTGCTA GCCAAATTCA ATTAGCGCCA ATAGTTAGCT CTCGAAGTGAC 27060
TCACACTGCT GCAGAGCAGC GTGTTGGTCA CTGCTTTGCT GCAGCGGGTA TGGCAAGCCT 27120
ATTACACGGC TTAATTAACT TAAATACTGT AGCCCAAACC AATAAAGCCA ATTGCGCGCT 27180
TATCAACAAT ATCAGTGAAA ACCAATTATC ACAGCTGTTG ATTAGCCAAA CAGCGAGCGA 27240
ACAAACAAGCA TTAACCGCGC GTTTAAGCAA TGAGCTTAAA TCCGATGCTA AACACCAACT 27300
GGTTAAGCAA GTCACCTTAG GTGGCCGTGA TATCTACCAG CATATTGTTG ATACACCGCT 27360
TGCAAGCCTT GAAAGCATTG CTCAGAAATT GCGCAAGCG ACAGCATCGA CAGTGTCAA 27420
CCAAGTTAAA CCTATTAAAG CCGCTGGCTC AGTCGAAATG GCTAACTCAT TCGAAACGGA 27480
AAGCTCAGCA GAGCCACAAA TAACAATTGC AGCACAACAG ACTGCAAAACA TTGGCGTCAc 27540

FIG. 4A-27

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CGCTCAGGCA ACCAAACGTG AATTAGGTAC CCCACCAATG ACAACAAATA CCATTGCTAA 27600
TACAGCAAAT AATTAGACA AGACTCTTGA GACTGTTGCT GGCAATACTG TTGCTAGCAA 27660
GGTTGGCTCT GCGGACALAG TCAATTTTCA ACAGAAACCA CAATTGGCTC AACAAAGCTCA 27720
CCTCGCCTTT CTTGAAAGCC GCAGTGCGGG TATGAAGGTG GCTGATGCTT TATTGAAAGCA 27780
ACAGCTAGCT CAAGTAACAG GCCAAACTAT CGATAATCAG GCCCTCGATA CTCAAAGCCGT 27840
CGATACTCAA ACAAGCGAGA ATGTAGCGAT TGCCGCAGAA TCACCAAGTTC AAGTTACAAC 27900
ACCTGTTCAA GTTACAACAC CTGTTCAAAT CAGTGTGTG GAGTTAAAAC CAGATCACGC 27960
TAATGTGCCA CCATACACGC CGCCAGTGCC TGCAATTAAAG CCGTGTATCT GGAACATATGC 28020
CGATTTAGTT GAGTACGCAG AAGGCGATAT CGCCAAGGTA TTTGGCAGTG ATTATGCCAT 28080
TATCGACAGC TACTCGCGCC GCGTACGTCT ACCGACCACT GACTACCTGT TGGTATCGCG 28140
CGTGACCAAA CTTGATGCGA CCATCAATCA ATTTAAGCCA TGCTCAATGA CCACTGAGTA 28200
CGACATCCCT GTTGATGCGC CGTACTTAGT AGACGGACAA ATCCCTTGGG CGGTAGCAGT 28260
AGAAATCAGG CAATGTGACT TGATGCTTAT TAGCTATCTC GGTATCGACT TTGAGAACAA 28320
AGGCGAGCGG GTTTATCGAC TACTCGATTG TACCCCTCACC TTCCTAGGCG ACTTGCCACG 28380
TGGCGGAGAT ACCCTACGTT ACGACATTAA GATCAATAAC TATGCTCGCA ACGGCGACAC 28440
CCTGCTGTTT TTCTTCTCGT ATGAGTGTTT TGTGGCGAC AAGATGATCC TCAAGATGGA 28500
TGGCGGCTGC GCTGGCTTCT TCACTGATGA AGAGTTGCC GACGGTAAAG GCGTGATTCTG 28560

FIG. 4A-28

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CACAGAAAGAA GAGATTAAAG CTCGCAGCCT AGTGCAAAAG CAACGCTTTA ATCCGTTACT 28620
AGATTGTCCT AAAACCCCAAT TTAGTTATGG TGATATTTCAT AAGCTATTAA CTGCTGATAT' 28680
TGAGGGTTGT TTTGGCCCAA GCCACAGTGG CGTCCACCAG CCGTCACTTT GTTTCGCATC 28740
TGAAAAAATTC TTGATGATTG AACAAAGTCAG CAAGGTTGAT CGCACTGGCG GTACTTGGGG 28800
ACTTGGCTTA ATTGAGGGTC ATAAGCAGCT TGAAGCAGAC CACTGGTACT TCCCATGTCA 28860
TTTCAAGGGC GACCAAGTGA TGGCTGGCTC GCTAATGGCT GAAGGTTGTG GCCAGTTATT 28920
GCAGTTCTAT ATGCTGCACC TTGGTATGCA TACCCAAACT AAAAATGGTC GTTTCCAACC 28980
TCTTGAAAAAC GCCTCACAGC AAGTACGCTG TCGCGGTCAA GTGCTGCCAC AATCAGGCGT 29040
GCTAACTTAC CGTATGGAAG TGACTGAAAT CGGTTTCAGT CCACGCCCAT ATGCTAAAGC 29100
TAACATCGAT ATCTTGCTTA ATGGCAAAGC GGTAGTGGAT TTCCAAAACC TAGGGGTGAT 29160
GATAAAAAGAG GAAGATGAGT GTACTCGTTA TCCACTTTTG ACTGAATCAA CAACGGCTAG 29220
CACTGCACAA GTAAACGCTC AAACAAGTGC GAAAAAGGTA TACAAGCCAG CATCAGTCAA 29280
TGCGCCATTA ATGGCACAAA TTCCTGATCT GACTAAAGAG CCAACAAGG GCGTTATTCC 29340
GATTTCCCAT GTTGAAGCAC CAATTACGCC AGACTACCCG AACCGGTGAC CTGATACAGT 29400
GCCATTACG CCGTATCACA TGTTTGAGTT TGCTACAGGC AATATCGAAA ACTGTTTCGG 29460
GCCAGAGTTC TCAATCTATC GCGGCATGAT CCCACCACGT ACACCATGCG GTGACTTACA 29520
AGTGACCACA CGTGTGATTG AAGTTAACGG TAAGCGTGGC GACTTTAAAA AGCCATCATC 29580

FIG. 4A-29

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GTGTATCGCT GAATATGAAG TGCCCTGCAGA TGGCTGGTAT TTCGATAAAA ACAGCCACGG 29640
CGCAGTGATG CCATATTCAA TTTTAATGGA GATCTCACTG CAACCTAACG GCTTTATCTC 29700
AGGTTACATG GGCACAACCC TAGGCTTCCC TGGCCTTGAG CTGTTCTTCC GTAACCTAGA 29760
CGGTAGCGGT GAGTTACTAC GTGAAGTAGA TTTACGTGGT AAAACCATCC GTAACGACTC 29820
ACGTTTATTA TCAACAGTGA TGGCCGGCAC TAACATCATC CAAAGCTTTA GCTTCGAGCT 29880
AAGCACTGAC GGTGAGCCTT TCTATCGCGG CACTGCGGTA TTTGGCTATT TTAAGGTGA 29940
CGCACTTAAA GATCAGCTAG GCCTAGATAA CCGTAAAGTC ACTCAGCCAT GGCATGTAGC 30000
TAACGGCGTT GCTGCAAGCA CTAAGGTGAA CCTGCTTGAT AAGAGCTGCC GTCACCTTAA 30060
TGCGCCAGCT AACCAGCCAC ACTATCGTCT AGCCGGTGGT CAGCTGAACT TTATCGACAG 30120
TGTTGAAATT GTTGATAATG GCGGCACCGA AGGTTTAGGT TACTTGTATG CCGAGCGCAC 30180
CATTGACCCA AGTGATTGGT TCTTCCAGTT CCACTTCCAC CAAGATCCGG TTATGCCAGG 30240
CTCCTTAGGT GTTGAAGCAA TTATTGAAAC CATGCAAGCT TACGCTATTA GTAAAGACTT 30300
GGGCGCAGAT TTCAAAAATC CTAAGTTTGG TCAGATTTTA TCGAACATCA AGTGGAAGTA 30360
TCGCGGTCAA ATCAATCCGC TGAACAAGCA GATGCTATG GATGTCAGCA TTACTTCAAT 30420
CAAAGATGAA GACGGTAAGA AAGTCATCAC AGGTAATGCC AGCTTGAGTA AAGATGGTCT 30480
GCGCATATAC GAGGTCTTCG ATATAGCTAT CAGCATCGAA GAATCTGTAT AAATCGGAGT 30540
GACTGTCTGG CTATTTTACT CAATTTCTGT GTCAAAAAGTG CTCACCTATA TTCATAGGCT 30600

FIG. 4A-30

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GGCGGCTTTT TTCTGGAAAT TGAGCAAAAG TATCTGCGTC CTAACTCGAT TTATAAGAAT 30660
GGTTTAATTG AAAAGAACAA CAGCTAAGAG CCGCAAGCTC AATATAAATA ATTAAGGGTC 30720
TTACAAATAA TGAATCCTAC AGCAACTAAC GAAATGCTTT CTCCGTGGCC ATGGGCTGTG 30780
ACAGAGTCAA ATATCAGTTT TGACGTGCAA GTGATGGAAC AACAACTTAA AGATTTTAGC 30840
CGGGCATGTT ACGTGGTCAA TCATGCCGAC CACGGCTTTG GTATTGGCA AACTGCCGAT 30900
ATCGTGA CTG AACAAAGCGC AACAGCACA GATTACCTG TTAGTGCTTT TACTCCTGCA 30960
TTAGGTACCG AAAGCCTAGG CGACAATAAT TTCCGCCGCG TTCACGGCGT TAAATACGCT 31020
TATTACGCAG GCGCTATGGC AAACGGTATT TCATCTGAAG AGCTAGTGAT TGCCCTAGGT 31080
CAAGCTGGCA TTTTGTGTGG TTCGTTTGA GCAGCCGGTC TTATTCCAAG TCGCGTTGAA 31140
GCGGCAATTA ACCGTATTCA AGCAGCGCTG CCAAATGGCC CTTATATGTT TAACCTTATC 31200
CATAGTCCTA GCGAGCCAGC ATTAGAGCGT GGCAGCGTAG AGCTATTTT AAAGCATAAG 31260
GTACGCACCG TTGAAGCATC AGCTTTCTTA GGTCTAACAC CACAAATCGT CTATTACCGT 31320
GCAGCAGGAT TGAGCCGAGA CGCACAAAGT AAAGTTGTGG TTGGTAACAA GGTATCGCT 31380
AAAGTAAGTC GCACCGAAGT GGCTGAAAAG TTTATGATGC CAGCGCCCGC AAAAATGCTA 31440
CAAAAACTAG TTGATGACGG TTCAATTACC GCTGAGCAA TGGAGCTGGC GCAACTTGT 31500
CCTATGGCTG ACGACATCAC TGCAGAGGCC GATTACAGTG GCCATACTGA TAACCGTCCA 31560
TTAGTAACAT TGCTGCCAAC CATTTAGCG CTGAAAGAAG AAATTCAAGC TAAATACCAA 31620

FIG. 4A-31

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TACGACACTC CTATTCGTGT CGGTGTGGT GCGGTGTGG GTACGCCCTGA TGCAGCGCTG 31680
GCAACGTTTA ACATGGGCGC GCGTATATT GTTACCGGCT CTATCAACCA AGCTTGTGTT 31740
GAAGCGGCG CAAGTGATCA CACTCGTAAA TTA CTGCGCA CCACTGAAAT GGCCGATGTG 31800
ACTATGGCAC CAGCTGCAGA TATGTTGAG ATGGGCGTAA AACTGCAGGT GGTAAAGCGC 31860
GGCAGCTAT TCCCAATGCG CGCTAACAG CTATATGAGA TCTACACCCG TTACGATTCA 31920
ATCGAAGCGA TCCCATTTAGA CGAGCGTGAA AAGCTTGAGA AACAAAGTATT CCGCTCAAGC 31980
CTAGATGAAA TATGGGCAGG TACAGTGGCG CACTTTAAAG AGCGCGACCC TAAGCAAATC 32040
GAACGCGCAG AGGTAACCC TAAGCGTAAA ATGGCATTTGA TTTTCCGTTG GTACTTAGGT 32100
CTTTCTAGTC GCTGGTCAA CTCAGGCGAA GTGGGTCGTG AAATGGATTA TCAAATTTGG 32160
GCTGGCCCTG CTCTCGGTGC ATTTAACCA TGGGCAAAAG GCAGTTACTT AGATAACTAT 32220
CAAGACCGAA ATGCCGTCGA TTTGGCAAAG CACTTAATGT ACGGCGCGGC TTACTTAAAT 32280
CGTATTAACT CGCTAACGGC TCAAGGCGTT AAAGTGCCAG CACAGTTACT TCGCTGGAAG 32340
CCAAACCAA GAATGGCCTA ATACACTTAC AAAGCACCAG TCTAAAAAGC CACTAATCTT 32400
GATTAGTGGC TTTTTTTTATT GTGGTCAATA TGAGGCTATT TAGCCTGTAA GCCTGAAAAAT 32460
ATCAGCACTC TGACTTTTACA AGCAAATAT AATTAAGGCA GGGCTCTACT CATTATACT 32520
GCTAGCAAAC AAGCAAAGTTG CCCAGTAAAA CAACAAGGTA CCTGATTAT ATCGTCATAA 32580
AAGTTGGCTA GAGATTCGTT ATTGATCTTT ACTGATTAGA GTCGCTCTGT TTGGAAAAAG 32640

FIG. 4A-32

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GTTCCTCGTT ATCATCAAAA TACACTCTCA AACCTTTAAT CAATTACAAC TTAGGCTTTC 32700
TGCGGGCATT TTTATCTTAT TTGCCACAGC TGTATTGGCC TTTAGGTTTT GGGTGCAACT' 32760
ACCATTAATT GAGGCCTCAT TAGTTAAATT ATCTGAGCAA GAGCTCACCT CTTTAAATTA 32820
CGCTTTTCAG CAAATGAGAA AGCCACTACA AACCATTAAT TACGACTATG CGGTGTGGGA 32880
CAGAACCTAC AGCTATATGA AATCAAACTC AGCGAGCGCT AAAAGGTACT ATGAAAAACA 32940
TGAGTACCCA GATGATACGT TCAAGAGTTT AAAAGTCGAC GGAGTATTTA TATTCAACCG 33000
TACAAAATCAG CCAGTTTTTA GTAAAGGTTT TAATCATAGA AATGATATAC CGCTGGTCTT 33060
TGAATTAACT GACTTTAAAC AACATCCACA AAACATCGCA TTATCTCCAC AAACCAACA 33120
GGCACACCCA CCGGCAAGTA AGCCGTTAGA CTCCCCCTGAT GATGTGCCTT CTACCCATGG 33180
GGTTATCGCC ACACGATACG GTCCAGCAAT TTATAGCTCT ACCAGCATTT TAAAATCTGA 33240
TCGTAGCGGC TCCCAACTTG GTTATTAGT CTTTCATTAGG TTAATTGATG AATGGTTCAT 33300
CGCTGAGCTA TCGCAATACA CTGCCGCAGG TGTTGAAATC GCTATGGCTG ATGCCGCAGA 33360
CGCACAAATTA GCGAGATTAG GCGCAAACAC TAAGCTTAAAT AAAGTAACCG CTACATCCGA 33420
ACGGTTAATA ACTAATGTCG ATGGTAAGCC TCTGTTGAAG TTAGTGCTTT ACCATACCAA 33480
TAACCAACCG CCGCCGATGC TAGATTACAG TATAATAATT CTATTAGTGT AGATGTCATT 33540
TTTACTGATC CTCGCTTATT TCCTTTACTC CTACTTCTTA GTCAGGCCAG TTAGAAAGCT 33600
GGCTTCAGAT ATTAAAAAAA TGGATAAAG TCGTGAAATT AAAAAAGCTAA GGTATCACTA 33660

FIG. 4A-33

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CCCTATTACT GAGCTAGTCA AAGTTGGGAC TCACTTCAAC GCCCTAATGG GGACGATTCA 33720
GGAACAAACT AACAGCTTA ATGAACAAAGT TTTTATTGAT AAATTAACCA ATATTCCCAA 33780
TCGTCCGGCT TTTGAGCAGC GACTTGAAAC CTATTGCCAA CTGCTAGCCC GGCAACAAAT 33840
TGGCTTTACT CTCATCATTG CCGATGTGGA TCATTTTAAA GAGTACAACG ATACTCTTGG 33900
GCACCTTGCT GGGGATGAAG CATTAAATAA AGTGGCACAA ACACATATCG AACAGTTTAA 33960
CCGTGCAGAA GATATTGTG CCCGTTTTGG TGGTGAAGAA TTTATTATGT TATTTGAGA 34020
CATACCTGAT GAGCCCTTGC AGAGAAAGCT CGATGCGATG CTGCACCTCTT TTGCAGAGCT 34080
CAACCTACCT CATCCAAACT CATCAACCGC TAATTACGTT ACTGTGAGCC TTGGGGTTTG 34140
CACAGTTGTT GCTGTTGATG ATTTTGAATT TAAAAGTGAG TCGCATATTA TTGGCAGTCA 34200
GGCTGCATTA ATCGCAGATA AGGCGCTTTA TCATGCTAAA GCCTGTGGTC GTAACCAAGT 34260
GTCAAAAACT ACTATTACTG TTGATGAGAT TGAGCAATTA GAAGCAATAA AAATCGGTCA 34320
TCAAGCCTAA ACTCGTTCGA GTACTTTCCC CTAAAGTCAGA GCTATTTGCC ACTTCAAGAT 34380
GTGGCTACAA GGCTTACTCT TTCAAAAACCT GCATCAATAG AACACAGCAA AATACAATAA 34440
TTTAAGTCAA TTTAGCCTAT TAAACAGAGT TAATGACAGC TCATGGTCGC AACTTATTAG 34500
CTATTTCTAG CAATATAAAA ACTTATCCAT TAGTAGTAAC CAATAAAAAA ACTAATATAT 34560
AAAACTATTT AATCATTATT TTACAGATGA TTAGCTACCA CCCACCTTAA GCTGGCTATA 34620
TTCGCACTAG TAAAAATAAA CATTAGATCG GGTTCAGATC AATTTACGAG TCTCGTATAA 34680

FIG. 4A-34

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AATGTACAAT AATTCACCTTA ATTTAATACT GCATATTTT ACAAGTAGAG AGCGGTGATG 34740
AAACAAAATA CGAAAGGCTT TACATTAATT GAATTAGTCA TCGTGATTAT TATTCTCGGT 34800
ATACTTGCTG CTGTGGCACT GCCGAAATTC ATCAATGTTT AAGATGACGC TAGGATCTCT 34860
GGGATGAGCG GTCAGTTTTC ATCATTTGAA AGTGCCGTAA AACTATACCA TAGCGGTTGG 34920
TTAGCCAAAG GCTACAACAC TGCGGTTGAA AAGCTCTCAG GCTTTGGCCA AGGTAATGTT 34980
GCATCAAGTG ACACAGGTTT TCCGTACTCA ACATCAGGCA CGAGTACTGA TGTGCATAAA 35040
GCTTGTTGGT AACTATGGCA TGGCATTACC GATACAGACT TCACAATTGG TCGGTTAGT 35100
GATGGCGATC TAATGACTGC AGATGTCGAT ATTGCTTACA CCTATCGTGG TGATATGTGT 35160
ATCTATCGCG ATCTGTATT TATTCAGCGC TCATTACCTA CTAAGGTGAT GAACTACAAA 35220
TTTAAAACTG GTGAAATAGA AATTATTGAT GCTTTCTACA ACCCTGACGG CTCAACTGGT 35280
CAATTACCAT AAATTTGGCG CTTATCTAAG TTGTACTTGC TCTGACCGAC ACAATAAATG 35340
TCGTTTCTCA GCATATATCA AAATACACAG CAAAAATTG GGGTTAGCTA TATAGCTAAC 35400
CCCAAAATCAT ATCTAACTTT ACACTGCATC TAATTCCAAA CAGTATCCAG CCAAAAGCCT 35460
AAACTATTGT TGACTCAGCG CTAAAAATATG CGATGCAACA AACAAAGTCTT GGATCGCAAT 35520
ACCTGAGCTA TCAAAAATGG TCACCTCATC AGCATTGTA CGTCCTGTTG CGGACTCGTT 35580
TATCACCTGA CCAATCTCAA TTATCGGCGT ATTTCTGCTA TGTGAAACT CACCAATAAC 35640
AATAGATTGA GAAGCAAAGT CGCAAAACAA GCGAGCATGA CTATATAGGT CAGTTGGCAA 35700

FIG. 4A-35

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CTCTTGCTTA CCCACTTTAT CAGCGCCCAT TGCAGAAATA TGCCTTCCTG CTTGTACCCA 35760
CTGCGCTTCA AATAAAGGCG CTTGAGCTGT GGTGCTGTG ATAATAATAT CTGCTTGTTT 35820
ACAAGCAGCT TGTGCATCAC AAGCTTCGGC ATTAATGCCT TTTTCTAATA AACGCTTAAC 35880
CAAGTTTCA GTTTTGCTAG CACTACGGCC AACTACCAAT ACCTTAGTTA ATGAACGAAC 35940
CTTGCTCACT GCTAGCACTT CATATTCAGC CTGATGACCG GTACCAAAAA CAGTTAATAC 36000
CGTAGCATCT TCTCTCGCGA GGTAACCTAC TGCTACTGCA TCGGCAGCAC CAGTGCGGTA 36060
AGCATTAACG GTAGTGGCAG CAATCACCGN CTGCAACATA CCGGTTAATG GATCGAGTAA 36120
AAATACGTTA GTGCCGTGGC ATGGTAAACC ATGTTTATGG TTATCAGGCC AATAGCTGCC 36180
TGTTTTCCAG CCGACAAGGT TTGGCGTTGA AGCCGACTTT AATGAGAACA TTTTCATTAAG 36240
GTTGCGGCC TGTCGATTAA CTACCGGGAA CAAGTTGCT TTATCATCTA CGGCAGCGAC 36300
AAACGCTTCT TTAACAGCGA TATAAGCCAG CTCATGGGAG ATGAGCTTTG ATGTTTGGC 36360
TTCAGTTAAA TAGATCATAT TACCACCCCT GCACTCGATT CCAGATCTCA TAGCCACCAT 36420
TATCACCATC AGTATCAAAT ACATGGTACT GAGCGTGCAAT TGAAGCTGTT GCACAGGCGT 36480
GGTTCGGCAA AATATGTAGA CGACTACCTA CCGGGAACCTG CGCTAAAATCA ATAAACGCCG 36540
CATCAACTGC TTCAATAATG CCGTGCTCTT GATTAACAGT TATAACCTGT AGACCTGATA 36600
ACACGTGACC GCTGTCGTCA CACACTAAAC CATAACCACA ATCTTTTGGC TGCTCTGCAG 36660
TACCTCTATC ACCCGAAAGA GCCATCCAAC CCGCATCAAT GAAAATCCAG TTTTATCAG 36720

FIG. 4A-36

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GATTATGACC AATAACACTG GTCACTACCG TTGCGGCAAT ATCAGTTAAC TGACACACGT 36780
TTAGCCCTGC CATGACTAAA TCGAAGAAGG TGTACACACC CGCTCTAACC TCGGTGATCC 36840
CATCAAGGTT TTGATAGCTT TCGCGTGTG GTGTTGAACC AATACTAACG ATGTCACATT 36900
GCATACCCGC TCGCGGAATG CGTCAGCAGC TTGTACAGCC GCTGCAACTT CATTTTGGC 36960
CGCATCAATT AATTGCTGTT TTTCAAAACA TTGATATGAC TCACCAGCGT GAGTNAGTAC 37020
GCCGTGAAA CTCGCTGCGC CAGACGTTAG TATCTGAGCA ATTTCAATCA ACTTATCGGC 37080
TTCCGGTGGA ATACCACCAC GATGGCCATC ACAATCAATT TCAATTAATG CTGGTATTG 37140
GCAGTCATAA GAACCAACAGA AATGATTTAG CTGATGCGCT TGCTCAACAC TATCAAGTAA 37200
AACTCTTGCA TTAATACCTT GGTCCAACAT TTTAGCAATA CGCGGCAACT TACCATCGGC 37260
AATACCTACT GCATAAATAA TGTCTGTGA ACCTTTAGAT GCTAAGGCCT CGGCCTCTTT 37320
TACCGTTGAT ACAGTGACTG GTGAGTTTTT AGTGGGTAAT AAAAACTCGG CTGCTTCAAG 37380
TGATCTTAAC GTTTTAAAT GCGGTCCTAG GTTTGCACCT AATCCTTCAA TTTTTTGGCG 37440
TAGTTGACTG AGGTTATTAA TAAATACTGG CTTATTTACA TATAAAAACG GTGTATCAAT 37500
TGCTTGATAC TGACTTTGCT GAGTCGTGGA AAGTATTGA GTAGATGGCA TCTTTAATAT 37560
CCTAGTTTCAAT CAATCAATCT AACAAAGTTG ATGCCTAGCC ACAGTGGCTT GTATTTCATGA 37620
TGCTTTGGAA AATGCTTATA TTCAAAGTAT TTGAAAAGACA TCAAACTTCT TGTTTAATGC 37680
TCAGTATCCA CCAGCACGCA TTTATTTTAT ATTAACCTATT ATCAAGATAT AGATTAGGTT 37740

FIG. 4A-37

CAAACCAAAT GATTAGTACT GAAGATCTAC GTTTATCAG CGTAATCGCC AGTCATCGCA 37800
CCTTAGCTGA TGCCGCTAGA AACTAAATA TCACGCCACC ATCAGTGACA TTAAGGTTGC 37860
AGCATATTGA AAAGAAACTA TCGATTAGCC TGATC 37895

FIG. 4A-38

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6121

* MKQTLMAISI	MSLFSEFNALA	AQHEHDHITV	DYEGKAATEH
TIAHNQAVAK	TLNFADTRAF	EQSSKNLVAK	FDKATADILR
AEFAFISDEI	PDSVNPSLYR	QAQLNMVPNG	YKVSDGIYQV
RGTDLSNLT	IRSDNGWIAY	DVLLTKEAAK	ASLQFALKNL
PKDGDVPVAM	IYSHSHADHF	GGARGVQEMF	PDVKVYGSDN
ITKEIVDENV	LAGNAMSRRRA	AYQYGATLGK	HDHGIVDAAL
GKGLSKGEIT	YVAPDYTLNS	EGKWETLTID	GLEMVFMDAS
GTEAESEMIT	YIPSKKALWT	AELTYQGMHN	IYTLRGAKVR
DALKWSKDIN	EMINAFGQDV	EVLFLASHSAP	VWGNQAINDF
LRLQORDNYGL	VHNQTLRLAN	DGVGIQDIGD	AIQDTIPESI
YKTWHTNGYH	GTYSHNAKAV	YNKYLGYFD	MNPANLNPLP
TKQESAKFVE	YMGGAADAIK	RAKDDYAQGE	YRFVATALNK
VVMAEPENDS	ARQLLADTYE	QLGYQAEGAG	WRNIYLTGAQ
ELRVGIQAGA	PKTASADVIS	EMDMPTLFDF	LAVKIDSQQA
AKHGLVKMNV	ITPDTKDILY	IELSNGNLSN	AVVDKEQAAD
ANLMVNKADV	NRILLGQVTL	KALLASGDAK	LTGDKTAFSK
IADSMVEFTP	DFEIVPTPVK		

*
8103

FIG. 4B

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8186

*
STKASARVVA KFNVEEAAIS IQQCQGISLA FRYSDDLHGL
LCHWNDAANM QQEKAEILGL GSKQPEANPK NSSSELLALG
IDQKLLVQRQ NLQHEVKHDA IADSIDVCHS LSKPANVGLF
TESLASFDFA FSKLSLALGL GKAKIYSEKL AWLDFFRDRQ
LAEPLALLAR KESESFYHSL ISHINTSNRC REIDVGFEIS
ASDTEEKSAQ SAGKNDATCI GVLLWDGSHS VNFHVGQTQAF
QADSLRPKGK DGYEFRWENP RIESHQSLLA RLYGRVM

*
9016**FIG. 4C**

8186

*GCTAGTCTTA GCTGASRTHR YSAASRAGCT CGAACAACAG CTTTAAAATT
CACTTCTTCT GCTGCAATAC TTATTTGCTG AACTGACCA ATACTCAGTG
CAAAACGATA ACTATCATCA AGATGGAAAR GVAVAAAYSH ASNVAGGAAA
ASRGNGNCYS GNGYSRAAHA RGTYSRASA SHSCCCAGTA AACAAATGCCA
ATTATCAGCA GCGTTCATTT GCTGTTCTTT AGCCTCAATC AAACCTAAAC
CAGACTTTTG TGGCTCAGCG TTAGGCTTAT TAGGYCYSHS TRASNASAAA
AASNMTGNGN GYSAAGGYGY SRYSGNRGAA ASNRYSASNS RAACTCGACT
CTAGTAAAGC AAGACCAATA TCTTGTTTTA ACAAACCTG TCGCTGATTA
AGTTGATGCT CAACCTTGTG ATCCGCAATA GCATCGGAAA TSRSRGAAGY
ASGNYSVAGN ARGGNASNGN HSGVAYSHSA SAAAAASSRA TCAACACAAT
GGCTCAAGCT TTTAGGTGCA TTAACCTCAA GAAAAGTTTC GCTCAGTGCA
GAGAAGTCAA ACGCAAAAGA TTTTAGCGAT AATGCCAGCA SVACYSHSSR
SRYSRAAASN VAGYHTRGS RAASRHASHA AHSRYSSRAA CCAAGTCCTT
TCGCTTTAAT GTAAGACTCC TTGAGCGCCC ACAAATCAAA AAAGCGGTCT
CGCTGCAAGG CCTCTGGTAA CGCTAACAAG GCTCGCTTTT GYGYSAAYS
TYRSRGYSAA TRASHHARGA SARGGNAAGR AAAAARGYSG CTGATTCAGA
GAAATAATGA CTAAGAATAG AGTGGATATT GGTGCTGTTA CGGCAACGCT
CAATGTCGAC GCCAAACTCA ATACTAGCAG AGTCAGTTTC SRGSRHTYRH
SSRSRHSASN THRSRASNAR GCYSARGGAS VAGYHGSRAA SRASTHRGCT
CCTTGCTTGC CTGACTGGCG CCTTTATTAT CAGCAGTGCA AATGCCTACT
AATAGCCAAT CTCCACTATG ACTCACATTA AAGTGGACCC CGGTTTGAGY
SSRAAGNSRA AGYYSASNAS AATHRCYSGY VATRASGYSR HSSRVAASNH
HSVAGYTHRG NGCAAATTGC GCATCACTCA ATCTAGGCTT ACCTTTGTCTG

FIG. 4D-1

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CCATATTCAA AGCGCCATTC ATTGGGGCGT ATTTCACTAT GTTGTGACAA
TAAAGCGCGC AAAHGNAAS SRARGRYSGY YSASGYTYRG HARGTRGASN
RARGGSRHSG NSRAAARGAA TAGCCTCTTA CCATTAAACC TTGAGTTTTA
GCTTCTTGTT TAATGTAGCG ATTAACCTTA ATTAACCTCAT CTTCAGGCAG
CCATGACTTA ACCAACTCTY RGYARGVAMT GYGNTHRYSY AGGNYSTYRA
RGASNVAYSG ASGRTRSRYS VAGTGTAGTC TGGTTATCGC ACTCTTGTAT
TGTTAACGGA CAGAAGTATA AGGAAATCAA^{*}

9157

FIG. 4D-2

9681

*MSMFLNSKLS RSVKLAIASG LTASLAMPVF AEETAAEEQI ERVAVTGSRI
AKAELTQPAP VVSLSAEELT KFGNQDLGSV LAELPAIGAT NTIIGNNSN
SSAGVSSADL RRLGANRTL VLVNGKRYVAG QPGSAEVDLS TIPTSMISRV
EIVTGGASAI YGSDAVSGVI NVILKEDFEG FEFNARTSGS TESVGTQEH
FDILGGANVA DGRGNVTFYA GYERTKEVMA TDIRQFDAWG TIKNEADGGE
DDGIPDRLRV PRVYSEMINA TGVINAFGGG IGRSTFDSNG NPAAQQRDG
TNSFAFGSFP NGCDTCFNTE AYENYIPGVE RINVGSSFN DFTDNIQFYT
DFRYVKSDIQ QQFQPSFRFG NININVEDNA FLNDDL RQQM LDAGQTNASF
AKFFDELGNR SAENKRELFR YVGGFKGGFD ISETIFDYDL YYVYGETNNR
RKTLNDLIPD NFVAAVDSVI DPDTGLAACR SQVASAQGDD YTPASVNGS
DCVAYNPFGM GQASAEARDW VSADVTREDK ITQQVIGGTL GTDSEELFEL
QGGAIAMVVG FEYREETSGS TTDEFTKAGF LTSAATPDSY GEYDVTEYFV
EVNIPVLKEL PFAHEL SFDG AYRNADYSHA GKTEAWKAGM FYSPLQLAL
RGTVGEAVRA PNIAEAFSPR SPGFGRVSDP CDADNINDDP DRVSNCAALG
IPPGFQANDN VSVDTLSGGN PDLKPETSTS FTGGLVWTPT FADNLSFTVD
YYDIQIEDAI LSVATQTVAD NCV DSTGGPD TDFCSQVDRN PTYDIELVR
SGYLNAAALN TKGIEFQAAY SLDLESFNAP GELRFNLLGN QLELERLEF
QNRPEINDE KGEVGDPELQ FRLGIDYRLD DLSVSWNTRY IDSVV TYDVS
ENGGSPEDLY PGHIGSMTH DLSATYYINE NFMINGGVRN LFDALPPGYT
NDALYDLVGR RAFLGIKVM

*
12590

FIG. 4E

13040

*MAKINSEHLD EATITSNKCT QTETEARHRN ATTTPEMRRF IQESDLSVSQ
LSKILNISEA TVRKWRKRDS VENCNTPHH LNTTLTPLQE YVVVGLRYQL
KMPLDRLLKA TQEFINPNVS RSGLARCLKR YGVSRSVDIQ SPHVPMRYFN
QIPVTQGS DV QTYTLHYETL AKTLALPSTD GDNVVQVVSL TIPPKLTEEA
PSSILLGIDP HSDWIYLDIY QDGNTQATNR YMAYVLKHGP FHLRKLLVRN
YHTFLQRFPG ATQNRPSKD MPETINKTPE TQAPSGDS^{*}
13903

FIG. 4F

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13906

*
MSQTSKPTNS ATEQAQDSQA DSRLNKRLKD MPIAIVGMAS IFANSRYLKN
FWDLISEKID AITELPSTHW QPEEYYDADK TAADKSYCKR GGFLPDVDFN
PMEFGLPPNI LELTDSSQLL SLIVAKEVLA DANLPENYDR DKIGITLGVG
GGQKISHSLT ARLQYPVLKK VFANSGISDT DSEMLIKKFQ DQYVHWEENS
FPGSLGNVIA GRIANRFDG GMNCVVDAA AGSLAAMRMA LTELTEGRSE
MMITGGVCTD NSPSMYMSFS KTPAFTTNET IQPFDIDSKG MMIGEGIGMV
ALKRLEDAER DGDRIYSVIK GVGASSDGKF KSIYAPRPSG QAKALNRAYD
DAGFAPHTLG LIEAHGTGTA AGDAAEFAGL CSVFAEGNDT KQHIALGSVK
SQIGHTKSTA GTAGLIKAAL ALHHKVLPPPT INVSQSPKPL DIENSPFYLN
TETRPWLPRV DGTPRRAGIS SFGFGGTNFH FVLEEYNQEH SRTDSEKAKY
RQRQVAQSFL VSASDKASLI NELNVLAASA SQAEFILKDA AANYGVRELD
KNAPRIGLVA NTAEELAGLI KQALAKLAAS DDNAWQLPGG TSYRAAAVEG
KVAALFAGQG SQYLNMGRLD TCYYPEMRQQ FVTADKVFAA NDKTPLSOTL
YPKPVFNKDE LKAQEAILTN TANAQSAIGA ISMGQYDLFT AAGFNADMVA
GHSFGELSAL CAAGVISADD YYKLAFARGE AMATKAPAKD GVEADAGAMF
AIITKSAADL ETVEATIAKF DGVKVANYNA PTQSVIAGPT ATTADAAKAL
TELGKAINL PVSGAFHTEL VGHAQAPFAK AIDAAKFTKT SRALYSNATG
GLYESTAABI KASFKKHMLQ SVRFTSQLEA MYNDGARVFFV EFGPKNILQK
LVQGTLVNTE NEVCTISINP NPKVDSDLQL KQAAMQLAVT GVVLSIEDPY
QADIAAPAKK SPMSISLNAA NHISKATRAK MAKSLTGIV TSQIEHVIEE
KIVEVEKLVE VEKIVEKVVE VEKVVEVEAP VNSVQANAIQ TRSVVAPVIE
NQVVSKNKSP AVQSISGDAL SNFFAAQQQT AQLHQQFLAI PQQYGETFTT
LMTEQAKLAS SGVAIPESLQ RSMEQFHQLQ AQTLOSHTQF LEMQAGSNIA
ALNLLNSSQA TYAPAIHNEA IQSQVVQSQT AVQPVISTQV NHVSEQPTQA
PAPKAQPAPV TTAVQTAPAQ VVRQAAPVQA AIEPINTSVA TTTPSAFSAE

FIG. 4G-1

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TALSATKVQA TMLEVVAEKT GYPTMLELE MDMEADLGID SIKRVEILGT
VQDELPGLE LSPEDLAECR TLGEIVDYM SKLPAEGSMN SQLSTGSAAA
TPAANGLSAE KVQATMMSVV AEKTGYPTM LELEMDMEAD LGIDSIKRVE
ILGTVQDELP GLPELSPEDL AECRTLGEIV DYMNSKLADG SKLPAEGSMN
SQLSTSAAAA TPAANGLSAE KVQATMMSVV AEKTGYPTM LELEMDMEAD
LGIDSIKRVE ILGTVQDELP GLPELNPEDL AECRTLGEIV TYMNSKLADG
SKLPAEGSMH YQLSTSTAAA TPVANGLSAE KVQATMMSVV ADKTGYPTM
LELEMDMEAD LGIDSIKRVE ILGTVQDELP GLPELNPEDL AECRTLGEIV
DYMNSKLPAE GSANTSAAAS LNVSAVAAPQ AAATPVSNGL SAEKVQSTMM
SVVAEKTGYP TEMLELGMDM EADLGIDSIK RVEILGTVQD ELPGLEPNP
EDLAECRTLGEIVDYMNSKL ADGSKLPAEG SANTSATAAT PAVNGLSADK
VQATMMSVVA EKTGYPTM ELGMDMEAD LGIDSIKRVE LGTVQDELPG
LPELNPEDLA ECRTLGEIVS YMNSQLADGS KLSTSAAEGS ADTSAANAAK
PAAISAEPV ELPPHSEVAL KKLNAANKLE NCFAADASV INDDGHNAGV
LAEKLIKQGL KVAVVRLPKG QPQSPLSSDV ASFELASSQE SELEASITAV
IAQIETQVGA IGGFIHLQPE ANTEEQTAVN LDAQSFTVHS NAFLWAKLLQ
PKLVAGADAR RCFVTVSRID GGGFYLNTDA LKDAELNQAA LAGLTKTLSH
EWPQVFCRAL DIATDVDATH LADAITSELF DSQAQLPEVG LSLIDGKVN
VTLVAAEAAD KTAKAELNST DKILVTGGAK GVTFECALAL ASRSQSHFIL
AGRSELQALP SWAEGKQTSE LKSAAIAHII STGQKPTPKQ VEAAVWPVQS
SIEINAALAA FNKVGASA EY VSM DVTSAA ITAALNGRSN EITGLIHGAG
VLADKHIQDK TLAE LAKVYG TKVNLKALL AALEPSKIKL LAMFSSAAGF
YGNIGQSDYA MSNDILNKAA LQFTARNPQA KVMSFNWGPW DGGMVNPALK

FIG. 4G-2

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KMFTERGVYV IPLKAGAELE ATQLLAETGV QLLIGTSMQG GSDTKATETA
SVKKLNAGEV LSASHPRAGA QKTPLQAVTA TRLLTPSAMV FIEDHRIGGN
SVLPTVCAID WMREAASDML GAQVKVLDYK LLKGIVFETD EPQELTLELT
PDDSDEATLQ ALISCNGRPQ YKATLISDNA DIKQLNKQFD LSAKAITTA
ELYSNGTLFH GPRLQGIQSV VQFDDQGLIA KVALPKVELS DCGEFLPQTH
MGGSQPFAED LLLQAMLVWA RLKTGSASLP SSIGEFTSYQ PMAFGETGTI
ELEVIKHNKR SLEANVALYR DNGELSAMFK SAKITISKSL NSAFLPAVLA
NDSEAN

^{*}
22173

FIG. 4G-3

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22203

*
MPLRIALILL PTPQFEVNSV DQSVLASYQT LQPELNALLN SAPTPEMLSI
TISDDSDANS FESQLNAATN AINNGYIVKL ATATHALLML PALKAAQMRI
HPHAQLAAMQ QAKSTPMSQV SGELKLGANA LSLAQTNALS HALSQAKRNL
TDVSVNECFE NLKSEQQFTE VYSLIQQLAS RTHVRKEVNQ GVELGPKQAK
SHYWFSEFHQ NRVAAINFIN GQQATSYVLT QGSGLLAAKS MLNQQRMLFI
LPGNSQQQIT ASITQLMQQL ERLQVTEVNE LSLECQLELL SIMYDNLVNA
DKLTTRDSKP AYQAVIQASS VSAAKQELSA LNDALTALFA EQTNATSTNK
GLIQYKTPAG SYLTLTPLGS NNDNAQAGLA FVYPGVGTVY ADMLNELHQY
FPALYAKLER EGDLCAMLQA EDIYHLDPKH AAQMSLGDLA IAGVGSSYLL
TQLLTDEFNI KPNFALGYSM GEASMWASLG VWQNPHALIS KTQTDPLFTS
AISGKLTA VR QAWQLDDTAA EIQWNSFVVR SEAAPIEALL KDYPHAYLAI
IQGDTCVIAG CEIQCKALLA ALGKRGIAAN RVTAMHTQPA MQEHQNVMDF
YLQPLKAELP SEISFISAAD LTAKQTVSEQ ALSSQVVAQS IADTFCQTL D
FTALVHHAQH QGAKLFVEIG ADRQNCTLID KIVKQDGASS VQHQPCTVP
MNAKGSQDIT SVIKALGQLI SHQVPLSVQP FIDGLKRELT LCQLTSQQLA
AHANVDSKFE SNQDHLLQGE V

24515

FIG. 4H

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24518

*MSLPDNASNH LSNQKGASQ ASKTSKQSKI AIVGLATLYP DAKTPQEFWQ
NLLDKRDSRS TLTNEKLGAN SQDYQGVQGG SDRFYCNKGG YIENFSFNAA
GYKLPEQSLN GLDDSFLLWAL DTSRNALIDA GIDINGADLS RAGVVMGALS
FPTTRSNDLF LPIYHSAVEK ALQDKLGVKA FKLSPNAHT ARAANESSLN
AANGAIAHNS SKVVADALGL GGAQLSLDAA CASSVYSLKL ACDYLSTGKA
DIMLAGAVSG ADPFFINMGF SIFHAYPDHG ISVPFDASSK GLFAGEGAGV
LVLKRLEDAE RDNDKIYAVV SGVGLSNDGK GQFVLSNPVK GQVKAHERAY
AASDIEPKDI EVIECHATGT PLGDKIELTS METFFEDKLQ GTDAPLIGSA
KSNLGHLLTA AHAGIMKMIF AMKEGYLPPS INISDAIASP KKLFKGKPTLP
SMVQGWPDKP SNNHFGVRTR HAGVSFVGFG GCNAHLLLES YNGKGTVKA
ATQVPRQAEP LKVVGSLASHF GPLSSINALN NAVTQDGNFG IELPKKRWKG
LEKHSSELLAE FGLASAPKGA YVDNFELDFL RFKLPPNEDD RLISQQMLML
RVTDEAIRDA KLEPGQKVAV LVAMETELEL HQFRGRVNLH TQLAQSLAAM
GVSLSTDEYQ ALEAIAMDSV LDAAKLNQYT SFIGNIMASR VASLWDFNGP
AFTISAAEQS VSRCIDVAQN LIMEDNLDAV VIAAVDLSGS FEQVILKNAI
APVAIEPNLE ASLNPTSASW NVGEGAGAVV LVKNEATSGC SYGQIDALGF
AKTAETALAT DKLLSQATD FNKVKVIETM AAPASQIQLA PIVSSQVTHT
AAEQRVGHCF AAAGMASLLH GLLNLNTVAQ TNKANCALIN NISENQLSQL
LISQTASEQQ ALTARLSNEL KSDAKHQLVK QVTLGGRDIY QHIVDTPLAS
LESITQKLAQ ATASTVVNQV KPIKAAGSVE MANSFETESS AEPQITIAAQ
QTANIGVTAQ ATKRELGTPP MTTNTIANTA NNLDKTLETV AGNTVASKVG
SGDIVNFQQN QQLAQQAHLA FLESRSAGMK VADALLKQQL AQVTGQTIDN
QALDTQAVDT QTSENVIAIA ESPVQVTTTPV QVTTTPVQISV VELKPDHANV
PPYTPPVPAL KPCIWNYADL VEYAEGDIAK VFGSDYAIID SYSRRVRLPT
TDYLLVSRVT KLDATINQFK PCSMTTEYDI PVDAPYLV DG QIPWAVAVES
GQCDLMLISY LGIDFENKGE RVYRLDCTL TFLGDLPRGG DTLRYDIKIN
NYARNGDTLL FFFSYECFVG DKMILKMDGG CAGFFTDEEL ADGKGVIRTE

FIG. 4I-1

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EEIKARSLVQ KQRFNPLLDC PKTQFSYGDI HKLLTADIEG CFGPSHSGVH
QPSLCFASEK FLMIEQVSKV DRTGGTWGLG LIEGHKQLEA DHWYFPCHFK
GDQVMAGSLM AEGCGQLLQF YMLHLGMHTQ TKNGRFQPLE NASQQVRCRG
QVLPQSGVLT YRMEVTEIGF SPRPYAKANI DILLNGKÄVV DFQNLGVMIK
EEDECTRYPL LTESTTASTA QVNAQTSAKK VYKPASVNAP LMAQIPDLTK
EPNKGVIPIS HVEAPITPDY PNRVPDTPVF TPYHMFEFAT GNIENCFGPE
FSIYRGMIPP RTPCGDLQVT TRVIEVNGKR GDFKKPSSCI AEYEVPADAW
YFDKNSHGAV MPYSILMEIS LQPNGFISGY MGTTLGFPGL ELFFRNLDGS
GELLREVDLR GKTIRNDSRL LSTVMAGTNI IQSFSFELST DGEPPFYRGTA
VFGYFKGDAL KDQLGLDNGK VTQPWHVANG VAASTKVNLL DKSCRHFNAP
ANQPHYRLAG GQLNFIDSVE IVDNGGTEGL GYLYAERTID PSDWFFQFHF
HQDPVMPGSL GVEAIIETMQ AYAISKDLGA DFKNPKFGQI LSNIKWKYRG
QINPLNKQMS MDVSITSIKD EDGKKVITGN ASLSKDGLRI YEVFDIAISI
EESV

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30529

FIG. 4I-2

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*
MNPTATNEML SPWPWAVTES NISFDVQVME QQLKDFSRA
YVNHADHGF GIAQTADIVT EQAANSTDLP VSAFTPALGT
ESLGDNNFRR VHGVKYAYYA GAMANGISSE ELVIALGQAG
ILCGSFGAAG LIPSRVEAAI NRIQAALPNG PYMFNLIHSP
SEPALERGSV ELFLKHKVRT VEASAFGLGT PQIVYYRAAG
LSRDAQGKVV VGNKVIKVS RTEVAEKFMM PPAKMLQKL
VDDGSITAEQ MELAQLVPMA DDITAEADSG GHTDNRPLVT
LLPTILALKE EIQAKYQYDT PIRVGCGGGV GTPDAALATF
NMGAAYIVTG SINQACVEAG ASDHTRKLLA TTEMADVMTA
PAADMFMGV KLQVVKRGTL FPMRANKLYE IYTRYDSIEA
IPLDEREKLE KQVFRSSLDE IWAGTVAHFN ERDPKQIERA
EGNPKRKMAL IFRWYLGSS RWSNSGEVGR EMDYQIWAGP
ALGAFNQWAK GSYLDNYQDR NAVDLAKHLM YGAAYLNRIN
SLTAQGVKVP AQLLRWKPNQ RMA

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32358

FIG. 4J

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*
MRKPLQTINY DYAVWDR TYS YMKSNSASAK RYYEKHEY PD
DTFKSLKVDG VFIFNRTNQP VFSKGFNHRN DIPLVFELTD
FKQHPQONIAL SPQTKQAHPP ASKPLDSPDD VPSTHGVIAT
RYGPAIYYSS TSILKSDRSG SQLGYLVFIR LIDEWFIAEL
SQYTAAGVEI AMADAADAQL ARLGANTKLN KVTATSERLI
TNVDGKPLLK LVLYHTNNQP PPMLDYSIII LLVEMSFLLI
LAYFLYSYFL VRPVRKLASD IKKMDKSREI KKLRYHYPIT
ELVKVATHFN ALMGTIQEQT KQLNEQVFID KLTNIPNRRRA
FEQRLETYCQ LLARQQIGFT LIIADVDFHK EYNDTLGHLA
GDEALIKVAQ TLSQQFYRAE DICARFGGEE FIMLFRDIPD
EPLQRKLDAM LHSFAELNLP HPNSSTANYV TVSLGVCTVV
AVDDFEFKSE SHIIGSQAAL IADKALYHAK ACGRNQALSK
TTITVDEIEQ LEANKIGHQ

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34327

FIG. 4K

1
*
AATAGATCGACTCGCAAAAGTTGCTTAAGATAGTGTCAATATAGCTTCTTATTTGTA
AATATTGTTTTTTATGTGTAAACATGTTTAGTGTGTGTAAATGCTGTTAATTATCCT
TTTGGGATTGTAATAGCTGATGTTGCTGGCTAATGAGTACTTTTAGTTCGGCAATAT
CTTGCTTTAAATCGCTAACTTCAGTTTTTAATTCACCCACACTTGTTGTATTTTTAA
GGCTCTCTTCCCCACCATCGACAAACCAGGATGATATGAAACCGGTAAACGTACCAA
AGAGACCGACACCTGCAGTCATGAGTAATGCCGCAATGATACGTCCGCCAGTGGTGA
CGGGGTAGTAGTCACCGTAACCAACAGTCGTTATTGTCACAAATGACCACCAAAGTG
CGTCGATGCCGTTATTGATGTTACTGCCTACTTGATCCTGTTCTAACAATAAAATAC
CGATAGCACCAAAGGTGACAAGGATGAAGGATATCGCAGATACCAGCGAAAAGGTGG
CTTTAAACCGATGTTCAAAAATCATTTTTTAAGATAATTTTTTGATGAGCGTATATTCT
GAATAGATCTTAATACTCTAGCGATACGAATTATGCGAATAAACTGCAGTTGCTCGA
CCATCGGAATACTCGACAGTAGGTCAATCCAACCCCATTTTCATAAACTGAAATTTAT
TCTCAGCTTGGTGAAAGCGAATTACAAAGTCAGTGAAAAAGAATAAGCAAATCGTAT
TATCTACGCTCGTTAATATTTTCAGTGACGTTACTTGAAAAGGTAAAAATAAGTTGCA
GTAGTGATGATACGACCACATGAAGTGATAAAATAAGCATGAAAATCTGAAATGGAT
TTACATCACTGTTGTTTTTGGTGCCACTTTTAAGGTTTCGTTTTTCACAACTCTGCTGCC
TCGGTTCATTGATTTTTGTTAATATAAACCTTAGTCAGTAGCAAGACAAAATATATTT
ACATCAATGTCATCGTATTATTCAACCGCGCGTCGTGTATTCAGACCAAGATCGTTG
TATATGTTAGTCATGTAGCGATGAGATTATCATGCGACAGGAGAGAATTATGTTTGT
TATTATTTTTTACGTACCTAAAGTTAATGTTGAAGAAGTAAAACAGGCGTTATTTAA
CGTCGGAGCTGGCACCATCGGTGATTATGATAGTTGTGCTTGGCAATGTTTGGGGAC
TGGGCAGTTCCAACCTTTACTTGGTAGCCAGCCACATATTGGTAAGCTAAATGAGGT
TGAATTCGTTGATGAGTTTAGAGTAGAAATGGTTTGTGAGCAGAAAATGTAAGGGC
AGCAATAAATGCACTTATTGCTGCGCACCCTTATGAAGAACCTGCTTATCATATTCT
GCAAACATTGAATCTTGATGAGTTACCTTAAGTTAGATGCACTGCACTTAATTGGTT
CGCTGTGCTAGGTTAGCAATTAGCAATTTTGACCATGTTAGCGATAGTTTTGGCACA

FIG. 5-1

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AGTGATCGATATTAACTATCCGATTCAGATCCCATTTTACTGCTGAATTAGGTTT
CATTACACTTGTTCTAGTGGTTTTTCCCGACAGGTGTAACCTGTGTTACTTGCGTAAG
GTTGATAATCTCTACCGCATTGGCAGGAGTTACACCTGCACCAGGCATAATACTAAT
TCTACCATCTGCTTGGTTAACTAACGTTTGGATTAAGGCGCAGCCTTCTAGCGCTTG
AGCTTGTTGACCAGAGGTTAAAATACGCTCACAACCAGCAGTGATCAAGGTCTCCAA
GGCTTGTTGTGGATCATTACACAAGTCGAAAGCGCGGTGGAAGGTTACGCCGAGATC
ACGTGATGCCACCATTAAAGCGTTTTAAAGCTGGCTCGTCAATATTACCATCTGCTGT
TAACGCGCCAATAACGACCCCTTGGACACCGAGTAACTTCATGAATTTGATGTCGGA
AACCATAATATCAACTTCTTGTTTCGCTATATACAAAATCACCGGCGCGAGGGCGAAT
AATGGCATAAATGGGGATCGTTGCTAGATCAATAGACTTTTGTACAAAACCTGCGTT
GGCGGTCAAGCCACCTAATGCTAATGCCGAGCACAACTCAATACGATCGGCGCCAGA
TGCTTGAGCCGTCAGCAGTGATTCTATATTATCGACACATACTTCTATTGTCATTGT
CATATACTTCTCTTTAAAAAGTTTATTAAAAATAATAAAGCCAGCATAAGTCGTTTT
ATACAATATGAAAGGGGAAAAGGCGACTTAGCTCGCCTAGATCAATTATTATGGCAG
AATACTGCCGTATTGTGATTAGAAAGACAGTTTTTTAAGCTCAATAGCCGTTATCGC
GTTGTTATCTACCATCGTGTAACTTTTCTGGCCTGGGTGCTTTATTAACTGTTTC
AGTGGCTGGATTAGGGTGAAATGATTCTTTTTTCAAATCTGTTTTTTGTATTTGAA
CGTACCTGTAATGTCTTGCTGCTCACGAAGACGTACAAATATTGGTTGCGCATAGCT
TGGTAGTGCCGCATTGACATGTTGATAGAATTCAGACGCTGAAAATTCATGAATAGG
GCAATTCAAAGTCAGCGCGACCATGCCTGCTCGGCCATCGTGATGTGGGAGCTTGAC
ACCATAAGCCACACTTTGCTCAATTTGCACAAAATCGTTAACTTGAGCTTCTACTTG
CGTCGTGGCGACATTTTCACCTTTCCAGCGGAATGTATCACCTAATCTATCCACAAA
GGAAATATGGCGATAACCTTGGTAATGAACGAGATCGCCGGTATTAAAATAACAGTC
ACCGTCTTTTAATACTGACTTAAATAGCTTTTTATTACTTTTGTGTCATCGGTATA
ACCATCAAATGGTGAACGTTTAGTTATCTTTGTTAGCAGTAGCCCTGTTTCTCCCGT

FIG. 5-2

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TTTTACTTTGGTCATTTTCCCTTTTCGCATTATACACAGGTTTGTCAATTGTCAATATC
ATATTGTATGACGGTAAAAGCAAGTGGAGTAACCCCGCTGTATGCGGTAAGTTCAG
CGCATTGGAGAACACAAGATTACACTCACTGGCGCCATAGAATTCATTAATATGCTC
GATCCCAAACGTTGTTGGAAATGATCCCAAATTTCGGGGCGTAATCCATTACCTAT
GATTTTCTTTATATTATGCTGTTTGTCTTTATTGCTAGGCGGTACATTTAATAAATA
ACGGCAGAGCTCGCCGATGTAAGTAAACGCAGTGGCATTATGAGCACGAACTTCATC
CCAAAAGCGACTTGAACTGAATTTTTTCAGAAAGTGCGAGGGTTGCTGCGCTACCAA
CACGGCGCTTAATGACACTGTCAGTGCATTGTTATGGTATAGGGGGAGTGATAAATA
CAATACATCATCAGCTGTTAAGCGTAATGATGCCATCCCCATGCCTGCCATGGATTT
AAACCAACGGTGATGGCTCATTCCTTGCTGCTTTTGGCAGTCCAGTTTTTCCCGAGGT
AAAGATATAAAACGCGCAATGCTTAAGCTGTATTTGTGCTGTTGATTACAGGGTTCAA
TACTGAATATCCTGCGACTAGTGTAGATATGTTTTTATAACCATCACTCATGTCTGG
CGTTTCTAAAGCGGGTACGTAAAAGACATTCTGTTGTAATGTGATGACAAATTGGT
TTCAATATTATTAATGGCGGATGTGTATAGTTCATCTGCGATGAGTAATTTGGTATC
GACCACGCTAAGACTATGTTGAGGATTGAATCCCGTTGTGTCGTATTTATCATACA
AGCAATCGCGCCAAGCTTGACAACTGCGAGGGCAATAATGATGGTTTCAGGCCTGTT
ATCGAGCATGATGGCGACTTTATCATTTTTTACCAATGCCGTATTCATGAAGGAAATG
GGCATATTGATTTGCTTGCTTATTCAATGAATCGTAACTATAACGCTGGTCTTTAAA
TTGTATTGCGATCAAGTCAGAGTTATTGACAGCTTGCTGCTCTAGTAATAAACCAAT
AGACATAAAACGTTTCGGGCTTTGCTTGTTGTAAGTGCCATAAGCCTTTGATGATTGG
CTTTGGGGTTTTTAATAGATTGATGGTACTTTTCAGGAATTGTTTGCCGGTTATAAC
AGTCATAAGCTAATTCTTTTTATCAAGAAGAGGGGTTATGACACCAAATAAATGGGT
CACGCGTTGGTTTAATTTGGTTAGACTAAATGTGTTGTTTTGCTGTGATAATGCGAC
GTTCAAACAACTTGAGAAGGTAAAAAATAGCATTTTTTAAATTGAACATCAATACT
AATGTGTTGAATATCAATCAAGTTTTCTAACTGTGCGAGCACGCGTGCTTTAGCAAA

FIG. 5-3

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CATGCCATGTGCTATTGCTGTTTTAAACCCCATTAGTTTCGCTGGGATAAAATGTAA
ATGGATTGGATTTGTGTCTTTGGAGATATAAGCATATTTATATACGTCAAAGGACT
AAATTTAAACAATGAAATCGGCTCGTAAGCATAATTCGCTGGCGTATTTACTATTTT
CTCACCGCTGGAACGTTGAGATCGTTGGCACGTTTTTCGCTGTTTTCGTTTTCTGTAA
GAATGTCGATGTACACTCCCACGCAAATTGTCCATCTACAAACACATCAATATGAGT
ATCAATGAAACGTCCTGTATCCGTTATGTACTCCTTAATTACACGACATGTGCTCGT
CAATATCGCGTTTTAATGCTATCGGTTGATGTTGTGTTATGCGATTTTCGATAATGGAC
TAGTCCTAATATAGATATCGGAAATTGTGTTGATGTCATGAGTTTCATCAATAATGG
AAAGATCATCACAATGGATAAGTAACCGGTACATAGTTTGTGTTATTAAACCCACA
GCATTTAATATATTGCTTTAAATTTTCGCTGATCTATTTTTTGTCCACTGATACTAAA
TTGCTCAGTACACACTTGTGTGCGACCAAGTGTTTCATCAGTGTTTTAACAATTGTATT
GAECTACTGCTTTACATATAAAAGCGAGATAATCGGTTGCTTTGTTAACAGTGTTGAT
CTGGTTAGCGTGCAATTGAAATAATTCATATAAGAGTATGTAGCATTATGTTAATAT
TTTGTTTTGGAAGTTGAATTGGCGAATCCGTAATCGGTTTATGGCAGTTCGGTCAAA
TACTTCAGGTAACTCGTTACTCATACCATTGATAGTGTTAAAGTGATTGACTGAAT
AAAGAATAGAGCTAAAAGTGGAATAATTATGCAAGATGCGGGTATGTTATTACGCAT
TGCTTATGAGGCAATGAAAGAGTTAGAGGTTGATGTCATTGAAGTACTTTCTCGTTG
TAACATAAGTGAAGAAGTACTGAATGATAAGGATCTTCGCACACCTAATCATGCACA
AACACATTTTTGGCAAGTATTAGAAGACATATCACAAGATCCTAACATCGGCATTTTC
ACTTGGTGAGAGAATGCCAGTGTTACGGGGCAGGTATTACAGTATCTTTTTCTCAG
TAGTCCTACATTTGGTACTGGCTGGGAACGCGCAACAAAATACTTTTCGATTAATCAG
TGATGCGGCGAGTGTTTCTATCAAGATGGAAGGCTGTGAAGCGCGATTATCTGTGAA
CTTAGATGGTTTAGCGGAAGATGCGAATCGTCATTTGAATGATTGCCTAGTGATCGG
TGCATTTAAATTTTGTATTATGTGACAGAAGGCGAATTTAAAGTAAGCAAAATAGC
CTTTGCTCATGCTCGCCCGAAAGATATTACTGCCTATACCAATGTATTTACATGTCC

FIG. 5-4

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GATTGAGTTTGCTGCCGAAGATAATTATATTTATTTTCGATGCTGATTTACTCGAACG
TCCTTCTTCGCATGCGGAGCCTGAGCTATTGCGCTTACACGATCAGCTTGCAAGCCG
TAAAATAGCCAAGTTAGAAGTGAAGATTTAGTGGATAAAGTACGTAAGGTTATTGC
ACAACAACCTTGAGTCTGGTGTGGTGACTTTAGAAAGTATCGCCACTGAACTTGACAT
GAAACCACGTATGCTAAGAGCGAAGTTAGCTGACATTGATTATAACTTTAATCAAAT
ACTCGCTGATTTTCGTTGCGAGTTATCAAAAAAAGTGTGGCGAATACGGACGAGTC
TATTGATCAGATTGTCTATCTCACTGGTTTTCTGAACCAAGTACTTTTTATCGTGC
CTTTAAGCGCTGGGTAAAATGACGCCAATTGAATATCGCCGTAGCAAAGTTCGCGGT
TAGGCATGCTAATCAACACGAGTCCTAAAAATTGCTGCTTAGTGCATAGTGCATAG
TGCATAGTGCTAGTAAGCCAAGTACAAAGCGTTAAAGTTAAGTACTTGAGCGAACCA
TCAGACACCACTTACTAGATTAAGCACCTATTAATGATTGACCACAAATTCTGATCG
TATTGCCTGTGATCCCTGCAGCTTGAGGTTGCGCAAAAAAGCTATCGCTTCAGCAA
CATCAACTGGCTTACCACCTTGTTTTAATGAATTCATACGACGACCAGCTTCACGAA
CTGTAAATGGAATCGCTGCTGTCATTTTTGTTTTCAATAAAGCCTGGTGCAACAGCAT
TAATGGTGATGTATTTGTCTGCAAGCGGAGTTTGCAATTGCATCAACATAACCAATGA
CTGCGGCCTTAGACGTTGCATAATTAGTCTGACCAAAGTTACCCGCAATCCCACTCA
TCGAAGACACACAAACAATGCGGCCATAGTCGTTGAGCAGATCATCATTTAGCAGTC
GCTCATTGATTCTTTCCATTGCCGACAAGTTAATATCCATCAGTACATCCCAATGGT
TATCCGGCATACTGCTAGCGTTTTGTCTTTTGTACCCCGGCATTATGGACGATGA
TATCAAGCGACTGTTCTCGCACAAAGTCAGCAATGATATTTGGGGCGTCAGCAGCGG
TAATATCAGCAACAATGCTGCTACCTTTCAAGCAATGAGCTACTTTTTCAAGGTCCT
GTTTTAATGCCGGAATGTCTAAGCAAATAACATGTGCGCCATCACGGGCGAGTGTTT
CAGCAATAGCAGCCCCGATGCCACGTGATGCACCAGTGACAAGTGCTGTCTTTCCTT
GTAATGGTTTTGCCGTGTTACTTGTTTCGTTAATAACTTCGTTAATAACTTCGTTAA

FIG. 5-5

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TAACCTTCGTTAATAGCCCCATTAATCGAACCGGGTTTTACGTTAATAACCTGTGCTG
AGATATAGGCTGATTTTGCTGAGGTTAAGAAACGTAGCGGGGCCTCTAATAATTGCT
CACTACCAGGTTGTACATAGATAAGTTGACAGGTA CTACCATTCTTGCCTATTTCTT
TGGCGACACTGCGACAAAACCCTTCTAAAGATCTTTGTACAGTCGCGTAGCTTACAT
CGTCAAGATGTTCACTCGGATGACCTAACACGATCACTCTGCTGCATGGCGAGAGCT
GCTTAATTACAGGTTGAAAAAACGATGTAATGCACTTAATTGCTTGCTGTTCTTAA
TGCCTGAGGCGTCGAAGATAATACCGTTGAAGCGATCTGTTTTAGCGATAGCATTAA
GGCTAATAGGTGTCGCGACTAAAGACGTTTGATTAAATTCAATATTAAGATCGGCTA
ACGCTGACGTGTTATTAGGATAAGAAATCGTGACTTCAGCATCTTTAAATGTGTTAA
GAATGGGTTTAATTAATTTGCTGTTGCTGGCTGCGCCGATGAGTAAGTTGCCAGAGA
TGAGATCGGTTCCCTGATCGTAGCGTGTTAACGTAACCGGTCGTGGCAGATTAAGCG
CTTTAAATAAACCTGATGTCCACTTGCCATTAGCGAGTTTTGCGTATGTATCCGTCA
TTTTCTAATCCTTGTTATAGTGAACAGTTTGAATCTCGAAGATGTACATGTGTTAA
AATTATCTGATAGCTATGACTTATCTGCCACTACGTAATAATAAATAGACCAGTTCA
TTACATCGTTAATCGATATAGTATAACTAAATACTAAGTAAATTATAATGATAAGAC
TGTTATCGTACTCGGATCAAACCTCTGATCAGCAAATAATCAAATTAGAGTTTTTATT
TTAAACTTGTATCAACAATGTTACATTAATGTATCTTACGTCTAATGTGCTACGGGC
ATATTTAAGTCACTAAATTAAAGGAATAAACCATGACAGGTCAAACAATAAGAAGAG
TAGCAATTATCGGCGGTAACCGTATCCCGTTTGACGTTCAAATACAGCGTATTCAA
AACTAAGTAACCAAGATATGCTGACGGAACTATCCGTGGCTTGGTGGTTAAATATA
ACCTACGTGGTGAACAACTGGGGGAAGTTGTTGCTGGTGCGGTAATTAAGCATTCTC
GTGATTTTAACTTAACACGTGAAGCCGTGCTAAGTGCAGGTCTTGACCTGAAACGC
CTTGTTATGACATTCAACAAGCTTGTGGTACTGGTCTAGCTGCAGCTATCCAAGTAG
CAAACAAAATTGCGCTTGGTCAAATAGAAGCGGTATTGCTGGTGGTTCTGATACGA

FIG. 5-6

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CATCAGATGCACCGATTGCAGTCAGTGAAGGCATGCGTAGTGTATTACTTGAGCTTA
ATCGAGCTAAAACGGGTAAGCAACGTTTGAAAGCACTATCTCGTCTACGTCTAAAAC
ACTTTGCGCCACTAACGCCTGCAAATAAAGAGCCGCGTACCAAATGGCGATGGGCG
ATCATTGTCAAGTAACAGCGAAAGAGTGAATATCTCACGTGAAGCACAAAGATGCAT
TGGCCTGCGCAAGTCATCAAAAATTAGCTGCAGCATATGAAGAAGGTTTCTTTGATA
CGTTAGTTTCACCTATGGCCGGCTTAACGAAAGATAACGTATTACGCGCAGATACAA
CAGTTGAGAACTGGCTAAATTGAAACCTTGTTTTGATAAAGTAAACGGCACTATGA
CGGCGGGTAACAGTACTAACCTTACCGATGGAGCATCAGCTGTATTACTTGCAAGTG
AAGAATGGGCAGCGGCACATAACTTACCAGTACAAGCTTATCTAACATTTGGTGAAA
CGGCCGCTATCGACTTCGTTGATAAGAAAGAAGGTCTGTTAATGGCGCCTGCATACG
CAGTGCCAAAAATGTTGAAGCGTGCTGGCCTTACATTACAAGACTTCGATTACTATG
AAATACATGAAGCATTTGCTGCGCAGTTATTAGCAACGCTAGCAGCTTGGGAAGACG
AAAAATTCTGTAAAGAAAACTGGGTCTAGATGCTGCGCTTGTTCAATTGATATGA
CCAAGTTAAACGTGAAAGGGAGTAGCTTAGCCACGGGTACCCATTTGCCGCAACTG
GTGGTCGTGTTGTGCTACGCTAGCGCAATTACTTGATCAGAAAGGTTCAAGTCTGTG
GTTTGATCTCGATTTGTGCTGCTGGTGGTCAAGGTATCACGGCAATTTTAGAGAAAT
AAACGCACTGTTTATTATCTATTGATTAAGCTGTCCTGAGATACTGGATATTTTTAA
ATAAAACGCCAATACTGCAGAGTATTGGCGTTTTTTTGTAATACCAATTCCTATATA
ACGGTGCAATTTTAAACACTTAATTTCCGGCATTGGTATCATAAAAAAGCAGCACCGA
AGTGCTGCTTGATTGTAGATTAACCTATTAAAATAGAGAGGCTAGAATTAGTCTTCG
TATGCTTCATTATGTACGCCAGCTGCACGACCCGATGGATCAGCATTGTTTTTGAAA
CTTTCATCCCAAGCTAATGCTTCTACAGTTGAACAAGCAACGGATTTACCAAACGGT
ACGCATTTTCGCTGCTGAATCACCTGGGAAGTGATCTTCAAAGATGGCACGATAGTAG
TAACCTTCTTTGCTATCTGGTGTGTTAATTGGGAACCTAAATGCTGCACTTGCTAAC
ATTTGATCAGTTACCGCTTCTTCAACGTGTACTTTAAGTTGGTCAATCCAAGAATAA

FIG. 5-7

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CCAACACCATCAGAGAATTGTTCTTTTTGACGCCATACAATTTCTTCAGGTAGTAAA
TCTTCAAATGCTTCTCGAATGATGTTTTCTCAATGCGGTCGCCC GTGATCATTTTT
AGTTCAGGGTTTAGACGCATTGACGCATCAACAAATTCTTTATCTAAGAAAGGAACA
CGTGCTTCGATGCCCCAAGCTGCCATAGATTTGTTTGACGTAAGCAATCAAACATA
TGTAATTTATTTACTTTACGTACCGTCTCTTCATGGAATTCTTTTCGCATTTGGCGCT
TTGTGGAAGTACAAGTAACCACCGAACAGTTCATCAGCACCTTCACCAGAAAGCACC
ATCTTAATCCCCATGGCTTTAATTTTACGTGCCATTAGGTACATAGGGGTTGATGCA
CGAATTGTTGTTACATCGTAGGTTTCAATGTGGTAAATCACGTGCGGTAAAGCGTCG
ATACCTTCTTGACAGTAAATTCAATTGAATGATGGATAGTACCTAAGTGATCTGCC
ACTTTTTGTGCAGCGGCTAAATCTGGAGAACCATTTAGGCCTACAGAGAAAGAGTGT
AGTTGTGGCCACCATGCTTCGGTTTTACCACCGTCTTCAATACGACGTTTTGCATAC
TGTTGGGTGATTGCTGAAATAACAGATGAATCTAACCCGCCTGATAATAATACGCCG
TAAGGTACATCACACATTAATTGACGTTTAACTGCATCTTCCAAACCTTGCTTAACA
ACGCTTTTATCACCACCATTTTGTGCAACGTTATCAAATCTTTCCAATCACGTTGA
TAATAAGGCGTGACTACACCATCCTTACTCCACAGGTAATGACCTGCTGGGAATTCT
TCAATTTGAGTACAAATTGGCACTAGTGCTTTTCATTTT CAGAGGCAACATAAAAGTTA
CCGTGTTTCATCATAGCCCGTATAAAGAGGGATGATACCGATATGGTCACGGCCAATC
AGGTAAGCGTCCTCTGTTTCGT CATATAAAGCGAAAGCAAAAATACCATTTAGATCA
TCTAAAAATTGTGTGCCTTTTTCTTTATATAGCGCAAGTATCACTTCGCAATCTGAT
TCTGTTTGGAATTCAAAGTCTACGTT CAGCGTTTTCTTTAAATCTTGTGGTTATAA
ATTTACCATTAAACAGCAAGTACGTGTGTCTTTCTTCATTATATAGCGGCTGTGCA
CCATTATTTACATCGACAATAGCAAGACGTT CATGAACTAAAATAGCATTGTCACTT
GTATAGATACCTGACCAATCTGGGCCGCGGTGACGTAGTAACTTTGATAGTTCTAGT
GCTTGTTTCGCGAAGAGGTTTAATGTCTGATTTGATGTCTAGAATTCCGAATATTGAG

FIG. 5-8

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CACATAACTAATTCCTTCTGGGGCTGCGTCTGCAGCTAACTTTCTAAATAGTGTGTC
TAATTTGCCACATTGTAGATTTAATGCAAACATTAATGATAAAACATTTATAAAAAA
TGTAATTCAATGTGGAATCGATAATTTAATGGCTTAAAAGTGAAGATCCATTAATTG
TGATGGCGAGGTGATAGACCAATGTAGACCTTAATGAATAAAGCAGGCACGATTGAA
TCCATTCAACGCAAAGTGGTACTAACTATTGTTTTAAACGTTATAAATAGTGTTTTA
AAGGTTATAAGTAAATAATTTAAAAACAATAATAATCCACATGCATTAAATTTATCA
TGATAAACCGCTATATCTCAATGGCAATTTGGGATAAGTGTAATAATATATGTAAAT
GAATGAGTTGACTTGCTTTTTTTTACACTAAGTGATGAAATTAAAGCTAGATGTCGTT
GTTAGCATTGATTAATAACGTACTAAAATACGACATCTAGTATAGAAATTTAAAAAA
CAGTTGGTTTTGATAGCATAACTGCATAAACTAATCAGCTTATTGCTCTGTAATATTT
TTGTAATTTAAATAGGTTTAATAAAATTATATGTCTGATAAATATAAACCGTACGAC
CTTTCCTTTAAAAAGACGTTTTTGTCTGCCTAAGTTTTGGCCTGTGTGGTTCGGGGTG
TTTGCAATATACTTATTAGCTTTTATGCCAGTAAAGCCGCGTGATAAATTTGCTCGA
TTCATAGCGAAGAAATTGTTTAGTCTAAAAATGATGGCAAAGCGTAAAAAGGTAGCA
AAGATCAATTTATCTATGTGCTTCCCTGAAATGGATGATACGGAACAAGACCGTATA
ATCATGGTCAATCTAGTTACTTTTTGTCAAACCTATCTTAAGTTATGCAGAGCCAAGT
GCGCGTAGTCGTGCTTATAACCGTGACCGTATGATAGTGCATGGTGGCGAGAATTTA
TTTCCGCTACTTGAACAAGGTAAGGCTTGATCTTATTAGTGCCGCATAGCTTCGCT
ATTGATTTTGCAGGTTTACACATTGCTTCTTATGGCGCGCCATTTTGTACTATGTTT
AACAACTCTGAGAATGAGTTGTTGATTGGCTGATGACACGTCAACGCGCTATGTTT
GGAGGCACTGTTTATCACCGCAAGGCAGGGCTAGGGGCTCTAGTTAAATCACTTAAG
AGCGGTGAAAGCTGTTATTACTTACCTGATGAAGACCATGGACCTAAGCGTAGTGTA
TTTGCGCCTTTATTTGCGACTCAAAAAGCAACTTTACCTGTAATGGGCAAGCTAGCA
GAAAAAACAAATGCACTCGTTGTTCTGTTTATGCGGCATATAATGAATCACTAGGT
AAATTTGAAACCTTTATTTCGACCAGCAATGCAAACTTTCCATCAGAAAGCCCAGAA
CAAGATGCAGTGATGATGAATAAAGAGATTGAAGCCTTGATTGAATGTGGTGTGAT

FIG. 5-9

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CAATATATGTGGACACTTAGATTATTGAGAACACGTCCGGACGGTAAAAAATCTAC
TAATAAGTTTAATAAACACCATAATCTTCGTTGAATATGGTGTTTACCCCCCTGAA
TACCCCTCTAAATTAATAACAAAAAAGCCATTTACGTAACATCTAATGATGATTTAG
CCTGCACTTGCTTTGTTTTAGTCTTAAGAGCCTAATAAACTTGATCTAGGTATAGA
TTCTGTCCTTTCTTTACGTAACGCGATCTATTTTTTTTAACCGATAGTTGTTATAATT
AGTTTCATATGAAAGAGATATCGTTTCAGTAAAAGCTATTTTCGTTTCAATAGATAAT
TTATTTATAGTCATATTTTCTGTAATGACAATCATTTTCTCATCTAGACTATAGATA
AGAATACGAATTAAGTAAGAACATTAATTTTACAAGAATATAAAATATCCCATCGGA
GCTATAAGAATGAAAAAGACTAAAATTGTTTGTACAATTGGTCCAAAACTGAATCA
GTAGAGAACTAACAGAGCTTGTTAATGCAGGCATGAACGTTATGCGTTTAAATTTC
TCTCATGGTAACTTTGCTGAACATTCAGTGCGTATTCAAATATCCGTCAAGTAAGT
GAAACCTGAATAAGAAAATTGCTGTTTTACTGGATACTAAAGGTCCAGAAATCCGT
ACGATTAACTAGAAAACGGTGACGATGTAATGTTGACCGCTGGTCAGTCATTACG
TTTACAACAGACATTAACGTGGTAGGTAATAAAGACTGTGTTGCTGTAACATATGCT
GGTTTTGCTAAAGACCTTAATCCTGGTGCAATCATCCTTGTTGATGATGGTTTAATT
GAAATGGAAGTTGTTGCAACAACCTGACACTGAAGTTAAATGTACAGTATTAAATACT
GGTGCACTTGGTGAAAATAAAGGCGTTAACTTACCTAACATCAGTGTAGGTCTACCT
GCATTGTCAGAAAAAGATAAAGCTGATTTAGCGTTTGTTGTGAGCAAGAAGTTGAT
TTTGTTGCTGCATCATTTATTTCGTAAGGCTGATGATGTAAGAGAAATTCGTGAAATC
CTATTTAATAATGGTGCGGAAAACATTCAGATTATCTCGAAAATTGAAAACCAAGAA
GGTGTAGACAATTTTCGATGAAATCTTAGCTGAATCAGACGGTATCATGGTTGCTCGT
GGCGATCTCGGTGTTGAGATCCCAGTTGAAGAAGTGATCATGGCACAGAAGATGATG
ATCAAAAAATGTAATAAAGCAGGTAAAGTTGTAATTACTGCAACACAAATGCTTGAT
TCAATGATCAGTAACCCACGTCCAACACGTGCAGAAGCGGGCGATGTTGCCAATGCT
GTGCTTGACGGTACCGACGCGGTAATGCTTTCTGGTGAACTGCGAAAGGTAAATAC

FIG. 5-10

CCAGTTGAAGCTGTGTCTATCATGGCAAACATCTGTGAACGTACTGATAACTCAATG
TCTTCGGATTTAGGTGCGAACATTGTTGCTAAAAGCATGCGCATTACAGAAGCTGTG
TGTAAGGTGCGGTAGAAACAACAGAAAAATTGTGTGCTCCACTTATTGTTGTTGCA
ACTCGTGGCGGTAAATCAGCAAAATCTGTTCTGTAAATACTTCCCGAAAGCAAATATT
CTTGCTATCACAACAATGAAAAAGCAGCGCAACAGTTATGCCTAACTAAAGGCGTA
AGCAGCTGCATCGTTGAGCAGATTGATAGCACTGATGAGTTCTACCGTAAAGGTAAA
GAGCTTGCAATTAGCAACTGGTTTAGCTAAAGAAGGCGATATCGTTGTTATGGTATCA
GGTGC GTTAGTACCATCAGGTACAACGAATACGGCATCTGTTACCAACTTTAAGTT
GCCATATTGATATTATAAAAAAGAGAGCGTATGCTCTCTTTTTTTATATCTGTAGTT
TATATGTCTGTACAAAAAATGATAAAGAGTACATAAACTATTAATATAGCGTAATA
TATAATGATTAACGGTGATGAAAGGGTTAAATAAATGGATAGTGCTAAACATAAAAT
TGGCTTAGTCCTTTCTGGCGGTGGTGCGAAAGGTATTGCTCATCTTGGTGTATTAAA
ATACCTGTTAGAGCAAGATATAAGACCGAATGTAATTGCGGGTACAAGTGCTGGCTC
TATGGTTGGTGCACTTTATTGCTCAGGACTTGAGATTGATGACATTTTACAATTCTT
CATCGATGTAAACCTTTTTCTTGGAAGTTTACCCGTGCCCCGTGCTGGCTTTATAGA
CCCCGCAAAATTATATCCTGAAGTGCTAAATATATCCCCGAGGATAGCTTTGAGTA
CCTTCAACCTGAATTGCGCATTGTTGCCACCAACATGTTACTCGGTAAAGAGCATAT
ATTTAAAGATGGCTCCGTGATTAATGCCTTATTAGCATCAGCCAGCTACCCTTTAGT
TTTTTCTCCGATGATCATTGACGATCAAGTGTATTGAGATGGCGGTATTGTTAATCA
TTTCCCCGTGAGTGTCATTGAAGATGATTGCGATAAAATAATCGGCGTATACGTGTC
GCCCATTCTGTCAGGTGCAAGCTGACGAACTCTCGAGTATAAAAGACGTGGTATTACG
TGCGTTCACGCTGCAGGGTAGTGGTGCTGAATTAGATAAACTATCGCAATGTGATGT
GCAAAATTTATCCAGAAGCGCTATTGAATTACAATACGTTTGCAACCGATGAAAAATC
ATTACGGGAGATCTACCAGATTGGTTATGATGCTGCAAAAGATCAACATGACAACCT
TATGGCATTGAAAGAAAGTATCACCACCAGCGAGGTTAAAAAGAACGTCTTTAGCAA

FIG. 5-11

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ATGGTTTGGTGATAAACTTGCTAGCAACAGCGGCAAATAGCGGCCACACGGATTTA
TACACTAGGATAATGGGCGTTAATAGCCTCACTGTCGTTGTGTGGTCTCTAATTTTA
GCTAAATCTTGTGTTATACTGACTTCCTATTAATCATAAACGATTTATCACGGTAAA
CATGACTCAAATAAATAACCCGCTTCACGGCATGACACTCGAAAAAGTAATTAACAG
TCTCGTTGAACAATATGGCTGGGATGGTCTTGGATACTACATCAACATTTCGTTGCTT
TACTGAAAATCCAAGTGTTAAGTCTAGTCTTAAATTTTACGTAAAACCCCTTGGGC
ACGTGATAAAGTAGAAGCGCTATATATCAAAATGGTGACTGAAGGCTAACTGTCTCC
ACGCTAGCGAACCGCTGTTTATAGTTAATATAAGTACTATAAGCAGGGCTCGTTAAT
TCAGTATGTAATTAATCCTGAATACCTCCGCTTATTTCAACATTGTACTCTCTAGAT
AACACTCTCAACATTACACCTTCAACATCACAGCCTCCACATAACATCCGATGACAT
AGCCCTGTTATTTTTTACATTTATCTATATGCTATATATTTTAGCCATTTGATCAAT
TGAGTTAATTTCTGCAATGACAAAGATATAACCATCATCCAGTACAAATTTATTATGA
AGATACCGACCATTCTGGTGTTGTTTACCACCCTAACTTTTTTAAATACTTTGAACG
TGCACGTGAGCATGTGATAAATAGTGACTTACTAGCAACATTGTGGAATGAACGCGG
TTTAGGTTTTGCGGTGTATAAAGCCAATATGACTTTTCAGGATGGGGTTCGAATTTGC
TGAAGTGTGTGATATTCGCACTTCTTTTGTCTAGACGGTAAGTACAAAACGATCTG
GCGCCAAGAAGTATGGCGTCCGAATGCGACTAGGGCTGCCGTTATCGGTGATATTGA
AATGGTGTGCTTAGACAAACAAAACGTTTACAGCCCATCCCTGATGATGTGTTAGC
TGCAATGGTTAGTGAATAAATGGTTCATGCATAAATAGTTAATACATGATTCTGGCC
CGTCACGTTTACAGATAAGAGGCATCCGATGCCTCCTTCTTATTACCAATACTACTG
CTTATCCCTTTCTAACTATCTTTAGCGTCCATAACACACTGAGCATTATTTCTATTA
ATCAGTGATTGTGATTTAATTATCTTCTATATATGTAATTTAATGTAATTTTCAATT
TATTTTGTAGCTACATTAAGGCTTACGAATGTACGCTAAAATGAGATGTCAGACTAAT
TTTAGCTTATTAATCTGTTAGCCGTTTATATTTTATAAAGATGGGATTTAACTTAAA

FIG. 5-12

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TGCAATTAATTATGGCGTAAATAGAGTGAAAACATGGCTAATATTCACCTAAGTCCTG
AATTTTATATAAAGTTTAATCTGTTATTTTAGCGTTTACCTGGTCTTATCAGTGAGG
TTTATAGCCATTATTAGTGGGATTGAAGTGATTTTAAAGCTATGTATATTATTGCA
AATATAAATTGTAACAATTAAGACTTTGGACACTTGAGTTCAATTTGGAATTGATTG
GCATAAAATTTAAAACAGCTAAATCTACCTCAATCATTTTAGCAAATGTATGCAGGT
AGATTTTTTTTCGCCATTTAAGAGTACACTTGTACGCTAGGTTTTTGTGTTAGTGTGCA
AATGAACGTTTTTGATGAGCATTGTTTTTAGAGCACAAAATAGATCCTTACAGGAGCA
ATAACGCAATGGCTAAAAAGAACACCACATCGATTAAGCACGCCAAGGATGTGTTAA
GTAGTGATGATCAACAGTTAAATTCTCGCTTGCAAGAATGTCCGATTGCCATCATTG
GTATGGCATCGGTTTTTGCAGATGCTAAAACTTGGATCAATTCTGGGATAACATCG
TTGACTCTGTGGACGCTATTATTGATGTGCCTAGCGATCGCTGGAACATTGACGACC
ATTACTCGGCTGATAAAAAAGCAGCTGACAAGACATACTGCAAACGCGGTGGTTTCA
TTCCAGAGCTTGATTTTGATCCGATGGAGTTTGGTTTACCGCCAAATATCCTCGAGT
TAACTGACATCGCTCAATTGTTGTCATTAATTGTTGCTCGTGATGTATTAAGTGATG
CTGGCATTGGTAGTGATTATGACCATGATAAAATTGGTATCACGCTGGGTGTGCGTG
GTGGTCAGAAACAAATTTTCGCCATTAACGTGCGGCCTACAAGGCCCGGTATTAGAAA
AAGTATTAAAAGCCTCAGGCATTGATGAAGATGATCGCGCTATGATCATCGACAAAT
TTAAAAAAGCCTACATCGGCTGGGAAGAGAACTCATTCCCAGGCATGCTAGGTAACG
TTATTGCTGGTCGTATCGCCAATCGTTTTGATTTTGGTGGTACTAACTGTGTGGTTG
ATGCGGCATGCGCTGGCTCCCTTGACGCTGTTAAAATGGCGATCTCAGACTTACTTG
AATATCGTTTCAGAAGTCATGATATCGGGTGGTGTATGTTGTGATAACTCGCCATTCA
TGTATATGTCATTCTCGAAAACACCAGCATTTACCACCAATGATGATATCCGTCCGT
TTGATGACGATTCAAAGGCATGCTGGTTGGTGAAGGTATTGGCATGATGGCGTTTA
AACGTCTTGAAGATGCTGAACGTGACGGCGACAAAATTTATTCTGTACTGAAAGGTA
TCGGTACATCTTCAGATGGTCGTTTTCAAATCTATTTACGCTCCACGCCAGATGGCC
AAGCAAAAGCGCTAAAACGTGCTTATGAAGATGCCGGTTTTGCCCTGAAACATGTG

FIG. 5-13

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GTCTAATTGAAGGCCATGGTACGGGTACCAAAGCGGGTGATGCCGCAGAATTTGCTG
GCTTGACCAAACACTTTGGCGCCGCCAGTGATGAAAAGCAATATATCGCCTTAGGCT
CAGTTAAATCGCAAATTGGTCATACTAAATCTGCGGCTGGCTCTGCGGGTATGATTA
AGGCGGCATTAGCGCTGCATCATAAAATCTTACCTGCAACGATCCATATCGATAAAC
CAAGTGAAGCCTTGATATCAAAAACAGCCCGTTATACCTAAACAGCGAAACGCGTC
CTTGATGCCACGTGAAGATGGTATTCCACGTCTGTCAGGTATCAGCTCATTTGGTT
TTGGCGGCACCAACTTCCATATTATTTTAGAAGAGTATCGCCCAGGTCACGATAGCG
CATATCGCTTAAACTCAGTGAGCCAACTGTGTTGATCTCGGCAAACGACCAACAAG
GTATTGTTGCTGAGTTAAATAACTGGCGTACTAAACTGGCTGTCGATGCTGATCATC
AAGGGTTTGTATTTAATGAGTTAGTGACAACGTGGCCATTAAAAACCCCATCCGTTA
ACCAAGCTCGTTTAGGTTTTGTTGCGCGTAATGCAAATGAAGCGATCGCGATGATTG
ATACGGCATTGAAACAATTCAATGCGAACGCAGATAAAATGACATGGTCAGTACCTA
CCGGGGTTTACTATCGTCAAGCCGGTATTGATGCAACAGGTAAAGTGGTTGCGCTAT
TCTCAGGGCAAGGTTGCAATACGTGAACATGGGTCTGTAATTAACCTGTAACCTTCC
CAAGCATGATGCACAGTGCTGCGGCGATGGATAAAGAGTTCAGTGCCGCTGGTTTAG
GCCAGTTATCTGCAGTTACTTTCCCTATCCCTGTTTATACGGATGCCGAGCGTAAGC
TACAAGAAGAGCAATTACGTTTAAACGCAACATGCGCAACCAGCGATTGGTAGTTTGA
GTGTTGGTCTGTTCAAACGTTTAAAGCAAGCAGGTTTTAAAGCTGATTTTGCTGCCG
GTCATAGTTTCGGTGAGTTAACCGCATTATGGGCTGCCGATGTATTGAGCGAAAGCG
ATTACATGATGTTAGCGCGTAGTCGTGGTCAAGCAATGGCTGCGCCAGAGCAACAAG
ATTTTGATGCAGGTAAGATGGCCGCTGTTGTTGGTGATCCAAAGCAAGTCGCTGTGA
TCATTGATACCCTTGATGATGTCTCTATTGCTAACTTCAACTCGAATAACCAAGTTG
TTATTGCTGGTACTACGGAGCAGGTTGCTGTAGCGGTTACAACCTTAGGTAATGCTG
GTTTCAAAGTTGTGCCACTGCCGGTATCTGCTGCGTTCCATACACCTTTAGTTCGTC
ACGCGCAAAAACCATTTGCTAAAGCGGTTGATAGCGCTAAATTTAAAGCGCCAAGCA
TTCCAGTGTTTGCTAATGGCACAGGCTTGGTGCAATTCAAGCAAACCGAATGACATTA

FIG. 5-14

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AGAAAAACCTGAAAAACCACATGCTGGAATCTGTTCAATTCATTCATCAAGAAATTGACA
ACATCTATGCTGATGGTGGCCGCGTATTTATCGAATTTGGTCCAAAGAATGTATTAA
CTAAATTGGTTGAAAACATTCTCACTGAAAAATCTGATGTGACTGCTATCGCGGTTA
ATGCTAATCCTAAACAACCTGCGGACGTACAAATGCGCCAAGCTGCGCTGCAAATGG
CAGTGCTTGGTGTGCGATTAGACAATATTGACCCGTACGACGCCGTTAAGCGTCCAC
TTGTTGCGCCGAAAGCATCACCAATGTTGATGAAGTTATCTGCAGCGTCTTATGTTA
GTCCGAAAACGAAGAAAGCGTTTGCTGATGCATTGACTGATGGCTGGACTGTTAAGC
AAGCGAAAGCTGTACCTGCTGTTGTGTGTCACAACCACAAGTGATTGAAAAGATCGTTG
AAGTTGAAAAGATAGTTGAACGCATTGTGCAAGTAGAGCGTATTGTGCAAGTAGAAA
AAATCGTCTACGTTAATGCTGACGGTTCGCTTATATCGCAAATAATCAAGACGTTA
ACAGCGCTGTTGTTAGCAACGTGACTAATAGCTCAGTGAATCATAGCAGTGATGCTG
ACCTTGTTGCCTCTATTGAACGCAGTGTTGGTCAATTTGTTGCACACCAACAGCAAT
TATTAAATGTACATGAACAGTTTATGCAAGGTCCACAAGACTACGCGAAAACAGTGCG
AGAACGTACTTGCTGCGCAGACGAGCAATGAATTACCGGAAAGTTTAGACCGTACAT
TGTCTATGTATAACGAGTTCCAATCAGAAACGCTACGTGTACATGAAACGTACCTGA
ACAATCAGACGAGCAACATGAACACCATGCTTACTGGTGCTGAAGCTGATGTGCTAG
CAACCCCAATAACTCAGGTAGTGAATACAGCCGTTGCCACTAGTCACAAGGTAGTTG
CTCCAGTTATTGCTAATACAGTGACGAATGTTGTATCTAGTGTGAGTAATAACGCGG
CGGTTGCAGTGCAAACCTGTGGCATTAGCGCCTACGCAAGAAATCGCTCCAACAGTCG
CTACTACGCCAGCACCCGCATTGGTTGCTATCGTGGCTGAACCTGTGATTGTTGCGC
ATGTTGCTACAGAAGTTGCACCAATTACACCATCAGTTACACCAGTTGTGCGCAACTC
AAGCGGCTATCGATGTAGCAACTATTAACAAAGTAATGTTAGAAGTTGTTGCTGATA
AAACCGGTTATCCAACGGATATGCTGGAACCTGAGCATGGACATGGAAGCTGACTTAG
GTATCGACTCAATCAAACGTGTTGAGATATTAGGCGCAGTACAGGAATTGATCCCTG
ACTTACCTGAACTTAATCCTGAAGATCTTGCTGAGCTACGCACGCTTGGTGAGATTG
TCGATTACATGAATTCAAAGCCCAGGCTGTAGCTCCTACAACAGTACCTGTAACAA

FIG. 5-15

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GTGCACCTGTTTCGCCTGCATCTGCTGGTATTGATTTAGCCCAATCCAAAACGTAA
TGTTAGAAGTGGTTGCAGACAAAACCGGTTACCCAACAGACATGCTAGAACTGAGCA
TGGATATGGAAGCTGACTTAGGTATTGATTCAATCAAGCGTGTGGAAATCTTAGGTG
CAGTACAGGAGATCATAACTGATTTACCTGAGCTAAACCCTGAAGATCTTGCTGAAT
TACGCACCCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTGAAA
GTGCGCCAGTGGCGACGGCTCCTGTAGCAACAAGCTCAGCACCGTCTATCGATTTGA
ACCACATTCAAACAGTGATGATGGATGTAGTTGCAGATAAGACTGGTTATCCAACTG
ACATGCTAGAACTTGGCATGGACATGGAAGCTGATTTAGGTATCGATTCAATCAAAC
GTGTGGAAATATTAGGCGCAGTGCAGGAGATCATCACTGATTTACCTGAGCTAAACC
CAGAAGACCTCGCTGAATTACGCACGCTAGGTGAAATCGTTAGTTACATGCAAAGCA
AAGCGCCAGTCGCTGAGAGTGCGCCAGTAGCGACGGCTTCTGTAGCAACAAGCTCTG
CACCGTCTATCGATTTAAACCATATCCAAACAGTGATGATGGAAGTGGTTGCAGACA
AAACCGGTTATCCAGTAGACATGTTAGAACTTGCTATGGACATGGAAGCTGACCTAG
GTATCGATTCAATCAAGCGTGTAGAAATTTTAGGTGCGGTACAGGAAATCATTACTG
ACTTACCTGAGCTTAACCCTGAAGATCTTGCTGAACTACGTACATTAGGTGAAATCG
TTAGTTACATGCAAAGCAAAGCGCCCGTAGCTGAAGCGCCTGCAGTACCTGTTGCAG
TAGAAAGTGCACCTACTAGTGTAACAAGCTCAGCACCGTCTATCGATTTAGACCACA
TCCAAAATGTAATGATGGATGTTGTTGCTGATAAGACTGGTTATCCTGCCAATATGC
TTGAATTAGCAATGGACATGGAAGCCGACCTTGGTATTGATTCAATCAAGCGTGTTG
AAATTCTAGGCGCGGTACAGGAGATCATTACTGATTTACCTGAACTAAACCCAGAAG
ACTTAGCTGAACTACGTACGTTAGAAGAAATTGTAACCTACATGCAAAGCAAGGCGA
GTGGTGTTACTGTAAATGTAGTGGCTAGCCCTGAAAATAATGCTGTATCAGATGCAT
TTATGCAAAGCAATGTGGCGACTATCACAGCGGCCGCAGAACATAAGGCGGAATTTA
AACCGGCGCCGAGCGCAACCGTTGCTATCTCTCGTCTAAGCTCTATCAGTAAAATAA
GCCAAGATTGTAAAGGTGCTAACGCCTTAATCGTAGCTGATGGCACTGATAATGCTG

FIG. 5-16

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TGTTACTTGCAGACCACCTATTGCAAACCTGGCTGGAATGTAAGTGCATTGCAACCAA
CTTGGGTAGCTGTAACAACGACGAAAGCATTTAATAAGTCAGTGAACCTGGTGACTT
TAAATGGCGTTGATGAACTGAAATCAACAACATTATTACTGCTAACGCACAATTGG
ATGCAGTTATCTATCTGCACGCAAGTAGCGAAATTAATGCTATCGAATACCCACAAG
CATCTAAGCAAGGCCTGATGTTAGCCTTCTTATTAGCGAAATTGAGTAAAGTAACTC
AAGCCGCTAAAGTGCGTGGCGCCTTTATGATTGTTACTCAGCAGGGTGGTTCATTAG
GTTTTGATGATATCGATTCTGCTACAAGTCATGATGTGAAAACAGACCTAGTACAAA
GCGGCTTAAACGGTTTAGTTAAGACACTGTCTCACGAGTGGGATAACGTATTCTGTC
GTGCGGTTGATATTGCTTCGTCATTAACGGCTGAACAAGTTGCAAGCCTTGTTAGTG
ATGAACTACTTGATGCTAACACTGTATTAACAGAAGTGGGTATCAACAAGCTGGTA
AAGGCCTTGAACGTATCACGTAACTGGTGTGGCTACTGACAGCTATGCATTAACAG
CTGGCAATAACATCGATGCTAACTCGGTATTTTTAGTGAGTGGTGGCGCAAAGGTG
TAACTGCACATTGTGTTGCTCGTATAGCTAAAGAATATCAGTCTAAGTTCATCTTAT
TGGGACGTTCAACGTTCTCAAGTGACGAACCGAGCTGGGCAAGTGGTATTACTGATG
AAGCGGCGTTAAAGAAAGCAGCGATGCAGTCTTTGATTACAGCAGGTGATAAACCAA
CACCCGTAAAGATCGTACAGCTAATCAAACCAATCCAAGCTAATCGTGAAATTGCGC
AAACCTTGCTGCAATTACCGCTGCTGGTGGCCAAGCTGAATATGTTTCTGCAGATG
TAACTAATGCAGCAAGCGTACAAATGGCAGTCGCTCCAGCTATCGCTAAGTTCGGTG
CAATCACTGGCATCATTGATGGCGCGGGTGTGTTAGCTGACCAATTCATTGAGCAAA
AAACACTGAGTGATTTTGAGTCTGTTTACAGCACTAAAATTGACGGTTTGTTATCGC
TACTATCAGTCACTGAAGCAAGCAACATCAAGCAATTGGTATTGTTCTCGTCAGCGG
CTGGTTTCTACGGTAACCCCGGCCAGTCTGATTACTCGATTGCCAATGAGATCTTAA
ATAAAACCGCATACCGCTTTAAATCATTGCACCCACAAGCTCAAGTATTGAGCTTTA
ACTGGGGTCCTTGGGACGGTGGCATGGTAACGCCTGAGCTTAAACGTATGTTTGACC
AACGTGGTGTTTACATTATTCCACTTGATGCAGGTGCACAGTTATTGCTGAATGAAC

FIG. 5-17

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TAGCCGCTAATGATAACCGTTGTCCACAAATCCTCGTGGGTAATGACTTATCTAAAG
ATGCTAGCTCTGATCAAAAGTCTGATGAAAAGAGTACTGCTGTAAAAAGCCACAAG
TTAGTCGTTTATCAGATGCTTTAGTAACTAAAAGTATCAAAGCGACTAACAGTAGCT
CTTTATCAAACAAGACTAGTGCTTTATCAGACAGTAGTGCTTTTCAGGTAAACGAAA
ACCACTTTTTAGCTGACCACATGATCAAAGGCAATCAGGTATTACCAACGGTATGCG
CGATTGCTTGGATGAGTGATGCAGCAAAAGCGACTTATAGTAACCGAGACTGTGCAT
TGAAGTATGTCGGTTTCGAAGACTATAAATTGTTTAAAGGTGTGGTTTTTGTATGGCA
ATGAGGCGGCGGATTACCAAATCCAATTGTGCGCTGTGACAAGGGCGTCAGAACAGG
ATTCTGAAGTCCGTATTGCCGCAAAGATCTTTAGCCTGAAAAGTGACGGTAAACCTG
TGTTTCATTATGCAGCGACAATATTGTTAGCAACTCAGCCACTTAATGCTGTGAAGG
TAGAACTTCCGACATTGACAGAAAGTGTTGATAGCAACAATAAAGTAACTGATGAAG
CACAAGCGTTATACAGCAATGGCACCTTGTTCCACGGTGAAAGTCTGCAGGGCATTA
AGCAGATATTAAGTTGTGACGACAAGGGCCTGCTATTGGCTTGTGAGATAACCGATG
TTGCAACAGCTAAGCAGGGATCCTTCCCGTTAGCTGACAACAATATCTTTGCCAATG
ATTTGGTTTTATCAGGCTATGTTGGTCTGGGTGCGCAAACAATTTGGTTTAGGTAGCT
TACCTTCGGTGACAACGGCTTGGACTGTGTATCGTGAAGTGGTTGTAGATGAAGTAT
TTTATCTGCAACTTAATGTTGTTGAGCATGATCTATTGGGTTCACGCGGCAGTAAAG
CCCGTTGTGATATTCAATTGATTGCTGCTGATATGCAATTACTTGCCGAAGTGAAAT
CAGCGCAAGTCAGTGTGAGTGACATTTTGAACGATATGTCATGATCGAGTAAATAAT
AACGATAGGCGTCATGGTGAGCATGGCGTCTGCTTTCTTCATTTTTTAACATTAAAC
ATATTAATAGCTAAACGCGGTTGCTTTAAACCAAGTAAACAAGTGCTTTTAGCTATT
ACTATTCCAAACAGGATATTAAAGAGAATATGACGGAATTAGCTGTTATTGGTATGG
ATGCTAAATTTAGCGGACAAGACAATATTGACCGTGTGGAACGCGCTTTCTATGAAG
GTGCTTATGTAGGTAATGTTAGCCGCGTTAGTACCGAATCTAATGTTATTAGCAATG
GCCAAGAACAAGTTATTACTGCCATGACAGTTCCTTAACTCTGTGAGTCTACTAGCGC

FIG. 5-18

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AAACGAATCAGTTAAATATAGCTGATATCGCGGTGTTGCTGATTGCTGATGTAAAAA
GTGCTGATGATCAGCTTGTAGTCCAAATTGCATCAGCAATTGAAAAACAGTGTGCGA
GTTGTGTTGTTATTGCTGATTTAGGCCAAGCATTAAATCAAGTAGCTGATTTAGTTA
ATAACCAAGACTGTCTGTGGCTGTAATTGGCATGAATAACTCGGTTAATTTATCTC
GTCATGATCTTGAATCTGTAAGTCAACAATCAGCTTTGATGAAACCTTCAATGGTT
ATAACAATGTAGCTGGGTTCGCGAGTTTACTTATCGCTTCAACTGCGTTTGCCAATG
CTAAGCAATGTTATATATACGCCAACATTAAGGGCTTCGCTCAATCGGGCGTAAATG
CTCAATTTAACGTTGGAAACATTAGCGATACTGCAAAGACCGCATTGCAGCAAGCTA
GCATAACTGCAGAGCAGGTTGGTTTGTAGAAAGTGTGAGCAGTCGCTGATTCGGCAA
TCGCATTGTCTGAAAGCCAAGGTTTAAATGTCTGCTTATCATCATACGCAAACCTTTGC
ATACTGCATTAAGCAGTGCCCGTAGTGTGACTGGTGAAGGCGGGTGTTCACAGG
TCGCAGGTTTATTGAAATGTGTAATTGGTTTACATCAACGTTATATTCCGGCGATTA
AAGATTGGCAACAACCGAGTGACAATCAAATGTCACGGTGGCGGAATTCACCATTCT
ATATGCCTGTAGATGCTCGACCTTGGTTCCACATGCTGATGGCTCTGCACACATTG
CCGCTTATAGTTGTGTGACTGCTGACAGCTATTGTCATATTCTTTTACAAGAAAACG
TCTTACAAGAACTTGTTTTGAAAGAAACAGTCTTGCAAGATAATGACTTAACTGAAA
GCAAGCTTCAGACTCTTGAACAAAACAATCCAGTAGCTGATCTGCGCACTAATGGTT
ACTTTGCATCGAGCGAGTTAGCATTAAATCATAGTACAAGGTAATGACGAAGCACAAT
TACGCTGTGAATTAGAACTATTACAGGGCAGTTAAGTACTACTGGCATAAGTACTA
TCAGTATTAAACAGATCGCAGCAGACTGTTATGCCCGTAATGATACTAACAAAGCCT
ATAGCGCAGTGCTTATTGCCGAGACTGCTGAAGAGTTAAGCAAAGAAATAACCTTGG
CGTTTGCTGGTATCGCTAGCGTGTTTAAATGAAGATGCTAAAGAATGGAAAACCCCGA
AGGGCAGTTATTTTACCGCGCAGCCTGCAAATAAACAGGCTGCTAACAGCACACAGA
ATGGTGTCACCTTCATGTACCCAGGTATTGGTGCTACATATGTTGGTTTAGGGCGTG
ATCTATTTTCATCTATTCCACAGATTTATCAGCCTGTAGCGGCTTTAGCCGATGACA

FIG. 5-19

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TTGGCGAAAGTCTAAAAGATACTTTACTTAATCCACGCAGTATTAGTCGTCATAGCT
TTAAAGAACTCAAGCAGTTGGATCTGGACCTGCGCGGTAACCTTAGCCAATATCGCTG
AAGCCGGTGTGGGTTTTGCTTGTGTGTTTACCAAGGTATTTGAAGAAGTCTTTGCCG
TTAAAGCTGACTTTGCTACAGGTTATAGCATGGGTGAAGTAAGCATGTATGCAGCAC
TAGGCTGCTGGCAGCAACCGGGATTGATGAGTGCTCGCCTTGACAATCGAATACCT
TTAATCATCAACTTTGCGGCGAGTTAAGAACACTACGTCAGCATTGGGGCATGGATG
ATGTAGCTAACGGTACGTTTCGAGCAGATCTGGGAAACCTATAACCATTAAGGCAACGA
TTGAACAGGTCGAAATTGCCTCTGCAGATGAAGATCGTGTGTATTGCACCATTATCA
ATACACCTGATAGCTTGTTGTTAGCCGGTTATCCAGAAGCCTGTCAGCGAGTCATTA
AGAATTTAGGTGTGCGTGCAATGGCATTGAATATGGCGAACGCAATTCACAGCGCGC
CAGCTTATGCCGAATACGATCATATGGTTGAGCTATACCATATGGATGTTACTCCAC
GTATTAATACCAAGATGTATTCAAGCTCATGTTATTTACCGATTCCACAACGCAGCA
AAGCGATTTCCACAGTATTGCTAAATGTTTGTGTGATGTGGTGGATTTCCACGTT
TGGTTAATACCTTACATGACAAAGGTGCGCGGGTATTCATTGAAATGGGTCCAGGTC
GTTTCGTTATGTAGCTGGGTAGATAAGATCTTAGTTAATGGCGATGGCGATAATAAAA
AGCAAAGCCAACATGTATCTGTTCCGTGTGAATGCCAAAGGCACCAGTGATGAACTTA
CTTATATTCGTGCGATTGCTAAGTTAATTAGTCATGGCGTGAATTTGAATTTAGATA
GCTTGTTTAAACGGGTCAATCCTGGTTAAAGCAGGCCATATAGCAAACACGAACAAAT
AGTCAACATCGATATCTAGCGCTGGTGAGTTATACCTCATTAGTTGAAATATGGATT
TAAAGAGAGTAATTATGGAAAATATTGCAGTAGTAGGTATTGCTAATTTGTTCCCGG
GCTCACAAGCACCGGATCAATTTTGGCAGCAATTGCTTGAACAACAAGATTGCCGCA
GTAAGGCGACCGCTGTTCAAATGGGCGTTGATCCTGCTAAATATACCGCCAACAAAG
GTGACACAGATAAATTTTACTGTGTGCACGGCGGTTACATCAGTGATTTCAATTTTG
ATGCTTCAGGTTATCAACTCGATAATGATTATTTAGCCGGTTTAGATGACCTTAATC
AATGGGGGCTTTATGTTACGAAACAAGCCCTTACCGATGCGGGTTATTGGGGCAGTA

FIG. 5-20

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CTGCACTAGAAAACCTGTGGTGTGATTTTAGGTAATTTGTCATTCCCAACTAAATCAT
CTAATCAGCTGTTTATGCCTTTGTATCATCAAGTTGTTGATAATGCCTTAAAGGCGG
TATTACATCCTGATTTTCAATTAACGCATTACACAGCACCGAAAAAACACATGCTG
ACAATGCATTAGTAGCAGGTTATCCAGCTGCATTGATCGCGCAAGCGGCGGGTCTTG
GTGGTTCACATTTTGCCTGGATGCGGCTTGTGCTTCATCTTGTTATAGCGTTAAGT
TAGCGTGTGATTACCTGCATACGGGTAAAGCCAACATGATGCTTGCTGGTGCGGTAT
CTGCAGCAGATCCTATGTTTCGTAAATATGGGTTTCTCGATATTCGAAGCTTACCCAG
CTAACAATGTACATGCCCCGTTTGACCAAAATTACAAGGTCTATTTGCCGGTGAAG
GCGCGGGCATGATGGTATTGAAACGTCAAAGTGATGCAGTACGTGATGGTGATCATA
TTTACGCCATTATTAAAGGCGGCGCATTATCGAATGACGGTAAAGGCGAGTTTGTAT
TAAGCCCGAACACCAAGGGCCAAGTATTAGTATATGAACGTGCTTATGCCGATGCAG
ATGTTGACCCGAGTACAGTTGACTATATTGAATGTCATGCAACGGGCACACCTAAGG
GTGACAATGTTGAATTGCGTTCGATGGAAACCTTTTTCAGTCGCGTAAATAACAAAC
CATTACTGGGCTCGGTAAATCTAACCTTGGTCATTTGTTAACTGCCGCTGGTATGC
CTGGCATGACCAAAGCTATGTTAGCGCTAGGTAAAGGTCTTATTCCTGCAACGATTA
ACTTAAAGCAACCACTGCAATCTAAAAACGGTTACTTTACTGGCGAGCAAATGCCAA
CGACGACTGTGTCTTGGCCAACAACCTCCGGGTGCCAAGGCAGATAAACCGCGTACCG
CAGGTGTGAGCGTATTTGGTTTTGGTGGCAGCAACGCCCATTGTTATTACAACAGC
CAACGCAAACACTCGAGACTAATTTTAGTGTTGCTAAACCACGTGAGCCTTTGGCTA
TTATTGGTATGGACAGCCATTTTGGTAGTGCCAGTAATTTAGCGCAGTTCAAAACCT
TATTAAATAATAATCAAAATACCTCCGTGAATTACCAGAACAACGCTGGAAAGGCA
TGGAAAGTAACGCTAACGTCATGCAGTCGTTACAATTACGCAAAGCGCCTAAAGGCA
GTTACGTTGAACAGCTAGATATTGATTTCTTGCGTTTTAAAGTACCGCCTAATGAAA
AAGATTGCTTGATCCCGCAACAGTTAATGATGATGCAAGTGGCAGACAATGCTGCGA
AAGACGGAGGTCTAGTTGAAGGTCGTAATGTTGCGGTATTAGTAGCGATGGGCATGG

FIG. 5-21

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AACTGGAATTACATCAGTATCGTGGTCGCGTTAATCTAACCACCCAAATTGAAGACA
GCTTATTACAGCAAGGTATTAACCTGACTGTTGAGCAACGTGAAGAACTGACCAATA
TTGCTAAAGACGGTGTTCCTCGGCTGCACAGCTAAATCAGTATACGAGTTTCATTG
GTAATATTATGGCGTCACGTATTTTCGGCGTTATGGGATTTTTCTGGTCCTGCTATTA
CCGTATCGGCTGAAGAAACTCTGTTTATCGTTGTGTTGAATTAGCTGAAAATCTAT
TTCAAACCACTGATGTTGAAGCCGTTATTATTGCTGCTGTTGATTTGTCTGGTTCAA
TTGAAACATTACTTTACGTCAGCACTACGGTCCAGTTAATGAAAAGGGATCTGTAA
GTGAATGTGGTCCGGTTAATGAAAGCAGTTCAGTAACCAACAATATTCTTGATCAGC
AACAAATGGCTGGTGGGTGAAGGCGCAGCGGCTATTGTCGTTAAACCGTCATCGCAAG
TCACTGCTGAGCAAGTTTATGCGCGTATTGATGCGGTGAGTTTTGCCCTGGTAGCA
ATGCGAAAGCAATTACGATTGCAGCGGATAAAGCATTAACTTGCTGGTATCAGTG
CTGCTGATGTAGCTAGTGTGAAGCACATGCAAGTGGTTTTAGTGCCGAAAATAATG
CTGAAAAAACCGCGTTACCGACTTTATACCCAAGCGCAAGTATCAGTTCGGTGAAAG
CCAATATTGGTCATACGTTTAAATGCCTCGGGTATGGCGAGTATTATTAACGGCGC
TGCTGTTAGATCAGAATACGAGTCAAGATCAGAAAAGCAAACATATTGCTATTAACG
GTCTAGGTCGTGATAACAGCTGCGCGCATCTTATCTTATCGAGTTCAGCGCAAGCGC
ATCAAGTTGCACCAGCGCCTGTATCTGGTATGGCCAAGCAACGCCACAGTTAGTTA
AAACCATCAAACCTCGGTGGTCAGTTAATTAGCAACGCGATTGTTAACAGTGCAGATT
CATCTTTACACGCTATTAAAGCGCAGTTTGCCGGTAAGCACTTAAACAAAGTTAACC
AGCCAGTGATGATGGATAACCTGAAGCCCCAAGGTATTAGCGCTCATGCAACCAATG
AGTATGTGGTGACTGGAGCTGCTAACACTCAAGCTTCTAACATTCAAGCATCTCATG
TTCAAGCGTCAAGTCATGCACAAGAGATAGCACCAACCAAGTTCAAAATATGCAAG
CTACAGCAGCCGCTGTAAGTTCACCCCTTTCTCAACATCAACACACAGCGCAGCCCG
TAGCGGCACCGAGCGTTGTTGGAGTGAAGTGTGAAACATAAAGCAAGTAACCAAAATTC
ATCAGCAAGCGTCTACGCATAAAGCATTTTTAGAAAGTCGTTTAGCTGCACAGAAAA

FIG. 5-22

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ACCTATCGCAACTTGTTGAATTGCAAACCAAGCTGTCAATCCAAACTGGTAGTGACA
ATACATCTAACAATACTGCGTCAACAAGCAATACAGTGCTAACAAATCCTGTATCAG
CAACGCCATTAACTTGTGTCTAATGCGCCTGTAGTAGCGACAAACCTAACCAGTA
CAGAAGCAAAAGCGCAAGCAGCTGCTACACAAGCTGGTTTTTCAGATAAAAGGACCTG
TTGGTTACAACCTATCCACCGCTGCAGTTAATTGAACGTTATAATAAACAGAAAACG
TGATTTACGATCAAGCTGATTTGGTTGAATTGCTGAAGGTGATATTGGTAAGGTAT
TTGGTGCTGAATACAATATTATTGATGGCTATTCGCGTCGTGTACGTCTGCCAACCT
CAGATTACTTGTTAGTAACACGTGTTACTGAACTTGATGCCAAGGTGCATGAATACA
AGAAATCATACATGTGTACTGAATATGATGTGCCTGTTGATGCACCGTTCTTAATTG
ATGGTCAGATCCCTTGGTCTGTTGCCGTCGAATCAGGCCAGTGTGATTTGATGTTGA
TTTCATATATCGGTATTGATTTCCAAGCGAAAGGCGAACGTGTTTACCGTTTACTTG
ATTGTGAATTAACTTTCCTTGAAGAGATGGCTTTTGGTGGCGATACTTTACGTTACG
AGATCCACATTGATTTCGTATGCACGTAACGGCGAGCAATTATTATTCTTCTTCCATT
ACGATTGTTACGTAGGGGATAAGAAGGTACTTATCATGCGTAATGGTTGTGCTGGTT
TCTTTACTGACGAAGAACTTTCTGATGGTAAAGGCGTTATTCATAACGACAAAGACA
AAGCTGAGTTTAGCAATGCTGTAAATCATCATTACGCCGTTATTACAACATAACC
GTGGTCAATACGATTATAACGACATGATGAAGTTGGTTAATGGTGATGTTGCCAGTT
GTTTTGGTCCGCAATATGATCAAGGTGGCCGTAATCCATCATTGAAATTCTCGTCTG
AGAAGTTCTTGATGATTGAACGTATTACCAAGATAGACCCAACCGGTGGTCATTGGG
GACTAGGCCTGTTAGAAGGTCAGAAAGATTTAGACCCTGAGCATTGGTATTTCCCTT
GTCACTTTAAAGGTGATCAAGTAATGGCTGGTTCGTTGATGTCGGAAGGTTGTGGCC
AAATGGCGATGTTCTTCATGCTGTCTCTTGGTATGCATACCAATGTGAACAACGCTC
GTTTCCAACCACTACCAGGTGAATCACAACGGTACGTTGTCGTGGGCAAGTACTGC
CACAGCGCAATACCTTAACCTTACCGTATGGAAGTTACTGCGATGGGTATGCATCCAC
AGCCATTTCATGAAAGCTAATATTGATATTTTGCTTGACGGTAAAGTGGTTGTTGATT

FIG. 5-23

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TCAAAACTTGAGCGTGATGATCAGCGAACAAGATGAGCATTACAGATTACCTGTAA
CACTGCCGAGTAATGTGGCGCTTAAAGCGATTACTGCACCTGTTGCGTCAGTAGCAC
CAGCATCTTCACCCGCTAACAGCGCGGATCTAGACGAACGTGGTGTGTAACCGTTTA
AGTTTCCTGAACGTCCGTTAATGCGTGTTGAGTCAGACTTGTCTGCACCGAAAAGCA
AAGGTGTGACACCGATTAAGCATTTTGAAGCGCCTGCTGTTGCTGGTCATCATAGAG
TGCCTAACCAAGCACCGTTTACACCTTGGCATATGTTTGAGTTTTCGACGGGTAATA
TTTCTAACTGTTTCGGTCCTGATTTTGATGTTTATGAAGGTCGTATTCCACCTCGTA
CACCTTGTGGCGATTTACAAGTTGTTACTCAGGTTGTAGAAGTGCAGGGCGAACGTC
TTGATCTTAAAAATCCATCAAGCTGTGTAGCTGAATACTATGTACCGGAAGACGCTT
GGTACTTTACTAAAAACAGCCATGAAAACCTGGATGCCTTATTCATTAATCATGGAAA
TTGCATTGCAACCAAATGGCTTTATTTCTGGTTACATGGGCACGACGCTTAAATACC
CTGAAAAAGATCTGTTCTTCCGTAACCTTGATGGTAGCGGCACGTTATTAAAGCAGA
TTGATTTACGCGGCAAGACCATTGTGAATAAATCAGTCTTGGTTAGTACGGCTATTG
CTGGTGGCGCGATTATTCAAAGTTTACGTTTGATATGTCTGTAGATGGCGAGCTAT
TTTATACTGGTAAAGCTGTATTTGGTTACTTTAGTGGTGAATCACTGACTAACCAAC
TGGGCATTGATAACGGTAAAACGACTAATGCGTGTTTTGTTGATAACAATACCCCG
CAGCGAATATTGATGTGTTTGATTTAACTAATCAGTCATTGGCTCTGTATAAAGCGC
CTGTGGATAAACCGCATTATAAATTGGCTGGTGGTCAGATGAACTTTATCGATACAG
TGTCAGTGGTTGAAGGCGGTGGTAAAGCGGGCGTGGCTTATGTTTATGGCGAACGTA
CGATTGATGCTGATGATTGGTTCTTCCGTTATCACTTCCACCAAGATCCGGTGATGC
CAGGTTCAATTAGGTGTTGAAGCTATTATTGAGTTGATGCAGACCTATGCGCTTAAAA
ATGATTTGGGTGGCAAGTTTGCTAACCACGTTTTATTGCGCCGATGACGCAAGTTG
ATTGGAAATACCGTGGGCAAATTACGCCGCTGAATAAACAGATGTCACTGGACGTGC
ATATCACTGAGATCGTGAATGACGCTGGTGAAGTGCGAATCGTTGGTGATGCGAATC
TGTCTAAAGATGGTCTGCGTATTTATGAAGTTAAAAACATCGTTTTAAGTATTGTTG

FIG. 5-24

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AAGCGTAAAGGGTCAAGTGTAACGTGCTTAAGCGCCGCATTGGTTAAAGACGCTTTG
CACGCCGTGAATCCGTCCATGGAGGCTTGGGGTTGGCATCCATGCCAACAACAGCAA
GCTTACTTTAATCAATACGGCTTGGTGTCCATTTAGACGCCTCGAACTTAGTAGTTA
ATAGACAAAATAATTTAGCTGTGGAATGAATATAGTAAGTAATCATTCGGCAGCTAC
AAAAAAGGAATTAAGAATGTTCGAGTTTAGGTTTAAACAATAACAACGCAATTAAGT
GGCTTGGAAAGTAGATCCAGCGTCAGTTCATACACAAGATGCAGAAATTAAAGCAGC
TTTAATGGATCTAACTAAACCTCTCTATGTGGCGAATAATTCAGGCGTAACTGGTAT
AGCTAATCATACGTCAGTAGCAGGTGCGATCAGCAATAACATCGATGTTGATGTATT
GGCGTTTGCGCAAAAGTTAAACCCAGAAGATCTGGGTGATGATGCTTACAAGAAACA
GCACGGCGTTAAATATGCTTATCATGGCGGTGCGATGGCAAATGGTATTGCCTCGGT
TGAATTGGTTGTTGCGTTAGGTAAAGCAGGGCTGTTATGTTTCATTTGGTGCTGCAGG
TCTAGTGCCTGATGCGGTTGAAGATGCAATTCGTCTGATTCAAGCTGAATTACCAAA
TGGCCCTTATGCGGTTAACTTGATCCATGCACCAGCAGAAGAAGCATTAGAGCGTGG
CGCGGTTGAACGTTTCCTAAAACTTGGCGTCAAGACGGTAGAGGCTTCAGCTTACCT
TGGTTTAACTGAACACATTGTTTGGTATCGTGCTGCTGGTCTAACTAAAAACGCAGA
TGGCAGTGTTAATATCGGTAACAAGGTTATCGCTAAAGTATCGCGTACCGAAGTTGG
TCGCCGCTTTATGGAACCTGCACCGCAAAAATTACTGGATAAGTTATTAGAACAAAA
TAAGATCACCCCTGAACAAGCTGCTTTAGCGTTGCTTGTACCTATGGCTGATGATAT
TACTGGGGAAGCGGATTCTGGTGGTCATACAGATAACCGTCCGTTTTTAACATTATT
ACCGACGATTATTGGTCTGCGTGATGAAGTGCAAGCGAAGTATAACTTCTCTCCTGC
ATTACGTGTTGGTGCTGGTGGTGGTATCGGAACGCCTGAAGCAGCACTCGCTGCATT
TAACATGGGCGCGGCTTATATCGTTCTGGGTTCTGTGAATCAGGCGTGTTGAAGC
GGGTGCATCTGAATATACTCGTAACTGTTATCGACAGTTGAAATGGCTGATGTGAC
TATGGCACCTGCTGCAGATATGTTTGAAATGGGTGTGAAGCTGCAAGTATTAACG
CGGTTCTATGTTGCGATGCGTGCGAAGAACTGTATGACTTGTATGTGGCTTATGA

FIG. 5-25

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CTCGATTGAAGATATCCCAGCTGCTGAACGTGAGAAGATTGAAAAACAAATCTTCCG
TGCAAACCTAGACGAGATTTGGGATGGCACTATCGCTTTCTTTACTGAACGCGATCC
AGAAATGCTAGCCCGTGCAACGAGTAGTCCTAAACGTAAAATGGCACTTATCTTCCG
TTGGTATCTTGGCCTTTCTTCACGCTGGTCAAACACAGGCGAGAAGGGACGTGAAAT
GGATTATCAGATTTGGGCAGGCCCAAGTTTAGGTGCATTCAACAGCTGGGTGAAAGG
TTCTTACCTTGAAGACTATACCCGCCGTGGCGCTGTAGATGTTGCTTTGCATATGCT
TAAAGGTGCTGCGTATTTACAACGTGTAAACCAGTTGAAATTGCAAGGTGTTAGCTT
AAGTACAGAATTGGCAAGTTATCGTACGAGTGATTAATGTTACTTGATGATATGTGA
ATTAATTAAAGCGCCTGAGGGCGCTTTTTTTGGTTTTTA ACTCAGGTGTTGTA ACTC
GAAATTGCCCTTTCAAGTTAGATCGATTACTCACTCACAATATGTTGATATCGCAC
TTGCCATATACTTGCTCATCCAAAGCCCTATATTGATAATGGTGTTAATAGTCTTTA
ATATCCGAGTCTTTCTTCAGCATAATACTAATATAGAGACTCGACCAATGTTAAACA
CÀACAAAGAATATATTCTTGTGTACTGCCTTATTATTAACGAGTGCGAGTACGACAG
CTACTACGCTAAACAATTCGATATCAGCAATTGAACAACGTATTTCTGGTCGTATCG
GTGTGGCTGTTTTAGATACGCAAATAAACAAACGTGGGCTTACAATGGTGATGCAC
ATTTTCCGATGATGAGTACATTCAAAACCCTCGCTTGCGCGAAAATGCTAAGTGAAT
CGACAAATGGTAATCTGGATCCAGTACTAGCTCATTGATAAAGGCTGAAGAATTAA
TCCCTTGGTCACCAGTCACTAAAACGTTTGTGAATAACACTATTACAGTGGCGAAAG
CGTGTGAAGCAACAATGCTGACCAGTGATAATACCGCGGCTAATATTGTTTTACAGT
ATATCGGAGGCCCTCAAGGCGTTACTGCATTCTTGCGAGAAATTGGTGATGAAGAGA
GTCAGTTAGATCGTATAGAACCTGAATTGAATGAAGCTAAGGTCCGAGACTTGCGTG
ATACCACGACACCGAAAGCCATAGTTACCACGCTCAACAACTACTACTTGGTGATG
TTCTACTTGATTTGGATAAAAACCAACTTAAAACATGGATGCAAATAATAAAGTGT
CAGATCCTTTACTGCGTTCTATATTACCGCAAGGCTGGTTTATTGCCGACCGCTCAG
GTGCGGGTGGTAATGGTTCTCGAGGTATAACTGCTATGCTTTGGCACTCCGAGCGTC

FIG. 5-26

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AACCGCTAATCATCAGTATTTATTTAACCGAACTGAGTTAGCAATGGCAATGCGCA
ATGAGATTATTGTTGAGATCGGTAAGCTGATATTCAAAGAATACGCGGTGAAATAAT
AAGTTATTTTTTGATAATACTTTAACGAGCGTAGCTATCGAAGTGAGGGCGTCAATT
AGACACCTTTGCTTCCCCTACAAAATCTAATGTGTATTACCTCGGCTAGTACAATTG
CCCTAAGTTATTTCTGTCCAGCTTTGGCTTAGTGCAATTGCGTTAGCCAATGTGAAC
ACCAAGGGACTTTGTCGTACCATAACTACCAAGCGACTTTGTCGTTTTATCTTTTC
TTAGACAAACAGAGGTAAATGAGTGACGCCTTCCAAATCACAGGAATGAATCCGCA
TTTCAATAAAATCTAACCCGTACCAACTCCGTACAAGTTGATCTTTAGTTGTTTAA
ATCTATAATAAATTCAATTACGGAATTAATCCGTACAACCTGGAGGTTTTATGGCTAC
TGCAAGACTTGATATCCGTTTGATGAAGAAATCAAAGCTAAGGCTGAGAAAGCATC
AGCTTTACTCGGCTTAAAAAGTTTAAACCGAATACGTTGTTTCGCTTAATGGACGAAGA
TTCAACTAAAGTAGTTTCTGAGCATGAGAGTATTACCGTTGAAGCGAATGTATTGCA
CCAATTTATGGCTGCTTGTGATGAAGCGAAAGCCCCAAATAAAGCATTACTGAAGC
CGCTGTATTTACTCAGAATGGTGAGTTTAAGTGAGTTATTCCAAACGTTTCAAAGAA
CTGGATAAATCAAAACATGACAGAGCATCATTTGACTGTGGCGAAAAAGAGCTAAAT
GATTTTATCCAACTCAAGCAGCCAAACATATGCAAGCAGGTATTAGCCGCACTCTG
GTTTTACCTGCTTCTGCGCCGTTACCAACAAAAAATATCCAATTTGCTCATTTTAT
AGTATCGCGCCAAGCTCAATTAGCCGCGATACGTTACCACAAGCAATGGCTAAAAAG
TTACCACGTTATCCTATCCCTGTTTTTCTTTTGGCTCAACTTGCCGTCCATAAAGAG
TTTCATGGGAGTGGGTTAGGCAAAGTTAGCTTAATTAAAGCGTTAGAGTACCTTTGG
GAAATTAACCTCTCACATGAGAGCTTACGCCATCGTTGTTGATTGTTTAACTGAACAA
GCTGAGTCATTCTACGCTAAATATGGTTTCGACGTTCTCTGCGAAATAAATGGTCGA
GTAAGAATGTTTCATATCAATGAAAACAGTCAATCAGTTATTCACTTAACAGTAAGAG
TTAGTATAACAGTTGTATGAATTAAATTTATTATATTCGGTAATCTCATTGCGATCA
CGCTAGAAGTGCGAGCGGGTCAGACCGAGGCCACAATAGCAGCCGTTACGTTTAGGG

FIG. 5-27

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GATGACTTAAAAAGATAACTACTACGTGCGGATCCTAGAGGATTAAAGGTTTA
TGATTACACAACATTTATTTATTGTGCTTAATTTTTTCTATCCAATATGCGCAAGCTG
TAAATATCACTGAAGTAGACTTTTATGTCAGTGATGATATCCCTAAAGATGTTGCCA
AATTAAAGATAGGTGAATCCATAACGAACTCCAGCCTTATTCTAAGTAACTCATCTA
TTCCACTCTCGCGGGAGACGGGTAACATATATTACTCTTCATCAATTGCTAACTTGA
ACTATGACTCGATAGAATTTGTTATGGCTCAATTGATGGCCGAAGATTCCAGCCTTT
ACAAGATGCTGGTAAATAGCGATAGGTTGTCCGTGCTAGTAATGACATCTTCCCAGT
CCACAGATCTCTATGGCTCGACTTACTCGGCTTATTTTCCTAATGTTGCGGTCATCG
ATTTGAATTGTGACTCGCTAACTTTAGAACATGAGCTCGGCCATCTATACGGAGCTG
AACATGAAGAAATATATGACGACTATGTCTTCTATGCTGCGATATGTGGAGACTATA
CGACTATCATGAACTCTATGCAGCCTGAAATGAAAGAAAAACAAATGATAAAGGCAT
ATTCATTCCCTGAATTAAAAGTGGATGGCTTGCAAGTGCGGAAATGAAAATACGAATA
ACAAAAGGTTATTTTAGACAATATTGGTCGGTTTAGATAGGATTGGGATATTATTC
TCATTGCGCTCTACTTAGTGCTGTTATTATGAGTGCCAGTGCTTCTATCTACGATAT
TGGTCTTAACAAGTATTTATCTATAGACGCTAAGGTGTTATGTATTTAAGGGATGTT
CAAGATGAACTAGGTGTAAACGATGTATAGTTGTATAACATTTTTTCAACGGTTGG
AACGTTGATTCTATCGGGTAACAAGACCGCGACGATCCGCGATAAGTCCGATAGTC
ATTACTTAGTTGGTCAGATGTTAGATGCTTGTAAGTACGGAAGATAATCGGAAAATGT
GTCAAATAGAAATACTGAGCATTGAATATGTGACGTTTAGTGAATTAAACCGTGCGC
ACGCCAATGCTGAAGGTTTACCGTTTTTGTTTATGCTTAAGTGGATAGTTGAAAGA
TTTATCCGACTTCAAATGATTTATTTTTCATAAGTTTCAGAGTTGTAAGTATCGATA
TCTTATAAGTCTTAGTGACAAAACAGAACTATTTATAGCGCTCAAGAAGGCGATAA
TTTGATAATGAATTATCGCCTTGTTACTATTAAGAGACTTTAAATGACTGAGATATA
AGATATGACACGGAAGAACATATTGATCACAGGCGCAAGTTCAGGGTTGGGCCGAGG
TATGGCCATCGAATTTGCAAAATCAGGTCATAACTTAGCACTTTGTGCACGTAGACT

FIG. 5-28

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TGATAATTTAGTTGCACTGAAAGCAGAACTCTTAGCCCTCAATCCTCACATCCAAAT
CGAAATAAAACCTCTTGATGTCAATGAACATGAACAAGTCTTCACTGTTTTCCATGA
ATTCAAAGCTGAATTTGGTACGCTTGATCGTATTATTGTTAATGCTGGATTAGGCAA
GGGTGGATCC

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FIG. 5-29

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AAATGCAATTAATTATGGCGTAAATAGAGTGAAAACATGGCTAATATTCACCTAAGTC
CTGAATTTTATATAAAGTTTAATCTGTTATTTTAGCGTTTACCTGGTCTTATCAGTG
AGGTTTATAGCCATTATTAGTGGGATTGAAGTGATTTTTAAAGCTATGTATATTATT
GCAAATATAAATTGTAACAATTAAGACTTTGGACACTTGAGTTCAATTTCGAATTGA
TTGGCATAAAATTTAAACAGCTAAATCTACCTCAATCATTTTAGCAAATGTATGCA
GGTAGATTTTTTTTCGCCATTTAAGAGTACACTTGACGCTAGGTTTTTGTTTAGTGT
GCAAATGAACGTTTTGATGAGCATTGTTTTTAGAGCACAAAATAGATCCTTACAGGA
GCAATAACGCAATGGCTAAAAAGAACACCACATCGATTAAGCACGCCAAGGATGTGT
TAAGTAGTGATGATCAACAGTTAAATTCTCGCTTGCAAGAATGTCCGATTGCCATCA
TTGGTATGGCATCGGTTTTTGCAGATGCTAAAACTTGGATCAATTCTGGGATAACA
TCGTTGACTCTGTGGACGCTATTATTGATGTGCCTAGCGATCGCTGGAACATTGACG
ACCATTACTCGGCTGATAAAAAAGCAGCTGACAAGACATACTGCAAACGCGGTGGTT
TCATTCCAGAGCTTGATTTTGATCCGATGGAGTTTGGTTTACCGCCAAATATCCTCG
AGTTAACTGACATCGCTCAATTGTTGTCATTAATTGTTGCTCGTGATGTATTAAGTG
ATGCTGGCATTGGTAGTGATTATGACCATGATAAAATTGGTATCACGCTGGGTGTCTG
GTGGTGGTCAGAAACAAATTTTCGCCATTAACGTCGCGCCTACAAGGCCCGGTATTAG
AAAAAGTATTAAAAGCCTCAGGCATTGATGAAGATGATCGCGCTATGATCATCGACA
AATTTAAAAAGCCTACATCGGCTGGGAAGAGAACTCATTCCCAGGCATGCTAGGTA
ACGTTATTGCTGGTCGTATCGCCAATCGTTTTGATTTTGGTGGTACTAACTGTGTGG
TTGATGCGGCATGCGCTGGCTCCCTTGCAGCTGTTAAAATGGCGATCTCAGACTTAC
TTGAATATCGTTCAGAAGTCATGATATCGGGTGGTGTATGTTGTGATAACTCGCCAT
TCATGTATATGTCATTCTCGAAAACACCAGCATTTACCACCAATGATGATATCCGTC
CGTTTGATGACGATTCAAAGGCATGCTGGTTGGTGAAGGTATTGGCATGATGGCGT
TTAAACGTCCTGAAGATGCTGAACGTGACGGCGACAAAATTTATTCTGTACTGAAAG
GTATCGGTACATCTTCAGATGGTCGTTTCAAATCTATTTACGCTCCACGCCCAGATG
GCCAAGCAAAAGCGCTAAAACGTGCTTATGAAGATGCCGGTTTTGCCCTGAAACAT
GTGGTCTAATTGAAGGCCATGGTACGGGTACCAAAGCGGGTGATGCCGCAGAATTTG

FIG. 6-1

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CTGGCTTGACCAAACACTTTGGCGCCGCCAGTGATGAAAAGCAATATATCGCCTTAG
GCTCAGTTAAATCGCAAATTGGTCATACTAAATCTGCGGCTGGCTCTGCGGGTATGA
TTAAGGCGGCATTAGCGCTGCATCATAAAATCTTACCTGCAACGATCCATATCGATA
AACCAAGTGAAGCCTTGGATATCAAAAACAGCCCGTTATACCTAAACAGCGAAACGC
GTCCTTGGATGCCACGTGAAGATGGTATTCCACGTCTGTCAGGTATCAGCTCATTTG
GTTTTGGCGGCACCAACTTCCATATTATTTTAGAAGAGTATCGCCCAGGTCACGATA
GCGCATATCGCTTAAACTCAGTGAGCCAACTGTGTTGATCTCGGCAAACGACCAAC
AAGGTATTGTTGCTGAGTTAAATAACTGGCGTACTAACTGGCTGTCGATGCTGATC
ATCAAGGGTTTGTATTTAATGAGTTAGTGACAACGTGGCCATTAAAAACCCCATCCG
TTAACCAAGCTCGTTTAGGTTTTGTTGCGCGTAATGCAAATGAAGCGATCGCGATGA
TTGATACGGCATTGAAACAATTCAATGCGAACGCAGATAAAATGACATGGTCAGTAC
CTACCGGGGTTTACTATCGTCAAGCCGGTATTGATGCAACAGGTAAAGTGGTTGCGC
TATTCTCAGGGCAAGGTTGCAATACGTGAACATGGGTCGTGAATTAACCTGTAACT
TCCCAAGCATGATGCACAGTGCTGCGGCGATGGATAAAGAGTTCAGTGCCGCTGGTT
TAGGCCAGTTATCTGCAGTTACTTTCCCTATCCCTGTTTATACGGATGCCGAGCGTA
AGCTACAAGAAGAGCAATTACGTTTAACGCAACATGCGCAACCAGCGATTGGTAGTT
TGAGTGTTGGTCTGTTCAAAACGTTTAAGCAAGCAGGTTTTAAAGCTGATTTTGCTG
CCGGTCATAGTTTCGGTGAGTTAACCGCATTATGGGCTGCCGATGTATTGAGCGAAA
GCGATTACATGATGTTAGCGCGTAGTCGTGGTCAAGCAATGGCTGCGCCAGAGCAAC
AAGATTTTGATGCAGGTAAGATGGCCGCTGTTGTTGGTGATCCAAAGCAAGTCGCTG
TGATCATTGATACCCCTTGATGATGTCTCTATTGCTAACTTCAACTCGAATAACCAAG
TTGTTATTGCTGGTACTACGGAGCAGGTTGCTGTAGCGGTTACAACCTTAGGTAATG
CTGGTTTCAAAGTTGTGCCACTGCCGGTATCTGCTGCGTTCCATACACCTTTAGTTC
GTCACGCGCAAAAACCATTTGCTAAAGCGGTTGATAGCGCTAAATTTAAAGCGCCAA
GCATTCCAGTGTTTGCTAATGGCACAGGCTTGGTGATTCAAGCAAACCGAATGACA
TTAAGAAAAACCTGAAAAACCATGCTGGAATCTGTTCAATTCAATCAAGAAATTG

FIG. 6-2

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ACAACATCTATGCTGATGGTGGCCGCGTATTTATCGAATTGGTCCAAAGAATGTAT
TAACTAAATTGGTTGAAAACATTCTCACTGAAAAATCTGATGTGACTGCTATCGCGG
TTAATGCTAATCCTAAACAACCTGCGGACGTACAAATGCGCCAAGCTGCGCTGCAAA
TGGCAGTGCTTGGTGTCGCATTAGACAATATTGACCCGTACGACGCCGTTAAGCGTC
CACTTGTTGCGCCGAAAGCATCACCAATGTTGATGAAGTTATCTGCAGCGTCTTATG
TTAGTCCGAAAACGAAGAAAGCGTTTGCTGATGCATTGACTGATGGCTGGACTGTTA
AGCAAGCGAAAGCTGTACCTGCTGTTGTGTGTCACAACCACAAGTGATTGAAAAGATCG
TTGAAGTTGAAAAGATAGTTGAACGCATTGTGCAAGTAGAGCGTATTGTGCAAGTAG
AAAAAATCGTCTACGTTAATGCTGACGGTTCGCTTATATCGCAAATAATCAAGACG
TTAACAGCGCTGTTGTTAGCAACGTGACTAATAGCTCAGTGACTCATAGCAGTGATG
CTGACCTTGTTGCCTCTATTGAACGCAGTGTTGGTCAATTTGTTGCACACCAACAGC
AATTATTAAATGTACATGAACAGTTTATGCAAGGTCCACAAGACTACGCGAAAACAG
TGCAGAACGTACTTGCTGCGCAGACGAGCAATGAATTACCGGAAAGTTTAGACCGTA
CATTGTCTATGTATAACGAGTTCCAATCAGAAACGCTACGTGTACATGAAACGTACC
TGAACAATCAGACGAGCAACATGAACACCATGCTTACTGGTGCTGAAGCTGATGTGC
TAGCAACCCCAATAACTCAGGTAGTGAATACAGCCGTTGCCACTAGTCACAAGGTAG
TTGCTCCAGTTATTGCTAATACAGTGACGAATGTTGTATCTAGTGTCAGTAATAACG
CGGCGGTTGCAGTGCAAACCTGTGGCATTAGCGCCTACGCAAGAAATCGCTCCAACAG
TCGCTACTACGCCAGCACCCGCATTGGTTGCTATCGTGGCTGAACCTGTGATTGTTG
CGCATGTTGCTACAGAAGTTGCACCAATTACACCATCAGTTACACCAGTTGTGCGAA
CTCAAGCGGCTATCGATGTAGCAACTATTAACAAAGTAATGTTAGAAGTTGTTGCTG
ATAAAACCGGTTATCCAACGGATATGCTGGAACCTGAGCATGGACATGGAAGCTGACT
TAGGTATCGACTCAATCAAACGTGTTGAGATATTAGGCGCAGTACAGGAATTGATCC
CTGACTTACCTGAACTTAATCCTGAAGATCTTGCTGAGCTACGCACGCTTGGTGAGA
TTGTGCGATTACATGAATTCAAAAGCCCAGGCTGTAGCTCCTACAACAGTACCTGTAA

FIG. 6-3

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CAAGTGCACCTGTTTCGCCTGCATCTGCTGGTATTGATTTAGCCACATCCAAAACG
TAATGTTAGAAGTGGTTGCAGACAAAACCGTTACCCAACAGACATGCTAGAACTGA
GCATGGATATGGAAGCTGACTTAGGTATTGATTCAATCAAGCGTGTGGAAATCTTAG
GTGCAGTACAGGAGATCATAACTGATTTACCTGAGCTAAACCCTGAAGATCTTGCTG
AATTACGCACCCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTG
AAAGTGCGCCAGTGGCGACGGCTCCTGTAGCAACAAGCTCAGCACCGTCTATCGATT
TGAACCACATTCAAACAGTGATGATGGATGTAGTTGCAGATAAGACTGGTTATCCAA
CTGACATGCTAGAACTTGGCATGGACATGGAAGCTGATTTAGGTATCGATTCAATCA
AACGTGTGGAAATATTAGGCGCAGTGCAGGAGATCATCACTGATTTACCTGAGCTAA
ACCCAGAAGACCTCGCTGAATTACGCACGCTAGGTGAAATCGTTAGTTACATGCAA
GCAAAGCGCCAGTCGCTGAGAGTGCGCCAGTAGCGACGGCTTCTGTAGCAACAAGCT
CTGCACCGTCTATCGATTTAAACCATATCCAAACAGTGATGATGGAAGTGGTTGCAG
ACAAAACCGGTTATCCAGTAGACATGTTAGAAGTTGCTATGGACATGGAAGCTGACC
TAGGTATCGATTCAATCAAGCGTGTAGAAATTTTAGGTGCGGTACAGGAAATCATT
CTGACTTACCTGAGCTTAACCCTGAAGATCTTGCTGAACTACGTACATTAGGTGAAA
TCGTTAGTTACATGCAAAGCAAAGCGCCCGTAGCTGAAGCGCCTGCAGTACCTGTTG
CAGTAGAAAGTGCACCTACTAGTGTAACAAGCTCAGCACCGTCTATCGATTTAGACC
ACATCCAAAATGTAATGATGGATGTTGTTGCTGATAAGACTGGTTATCCTGCCAATA
TGCTTGAATTAGCAATGGACATGGAAGCCGACCTTGGTATTGATTCAATCAAGCGTG
TTGAAATTCTAGGCGCGGTACAGGAGATCATTACTGATTTACCTGAACTAAACCCAG
AAGACTTAGCTGAACTACGTACGTTAGAAGAAATTGTAACCTACATGCAAAGCAAGG
CGAGTGGTGTTACTGTAAATGTAGTGGCTAGCCCTGAAAATAATGCTGTATCAGATG
CATTTATGCAAAGCAATGTGGCGACTATCACAGCGGCCGCAGAACATAAGGCGGAAT
TTAAACCGGCGCCGAGCGCAACCGTTGCTATCTCTCGTCTAAGCTCTATCAGTAAAA
TAAGCCAAGATTGTAAAGGTGCTAACGCCCTTAATCGTAGCTGATGGCACTGATAATG
CTGTGTTACTTGCAGACCACCTATTGCAAACCTGGCTGGAATGTAAGTGCATTGCAAC
CAACTTGGGTAGCTGTAACAACGACGAAAGCATTTAATAAGTCAGTGAACCTGGTGA

FIG. 6-4

CTTTAAATGGCGTTGATGAACTGAAATCAACAACATTATTACTGCTAACGCACAAT
TGGATGCAGTTATCTATCTGCACGCAAGTAGCGAAATTAATGCTATCGAATACCCAC
AAGCATCTAAGCAAGGCCTGATGTTAGCCTTCTTATTAGCGAAATTGAGTAAAGTAA
CTCAAGCCGCTAAAGTGCGTGGCGCCTTTATGATTGTTACTCAGCAGGGTGGTTCAT
TAGGTTTTGATGATATCGATTCTGCTACAAGTCATGATGTGAAAACAGACCTAGTAC
AAAGCGGCTTAAACGGTTTAGTTAAGACACTGTCTCACGAGTGGGATAACGTATTCT
GTCGTGCGGTTGATATTGCTTCGTCATTAACGGCTGAACAAGTTGCAAGCCTTGTTA
GTGATGAACTACTTGATGCTAACTGTATTAACAGAAGTGGGTATCAACAAGCTG
GTAAAGGCCTTGAACGTATCACGTTAACTGGTGTGGCTACTGACAGCTATGCATTAA
CAGCTGGCAATAACATCGATGCTAACTCGGTATTTTGTAGTGAGTGGTGGCGCAAAG
GTGTAAGTGCACATTGTGTTGCTCGTATAGCTAAAGAATATCAGTCTAAGTTCATCT
TATTGGGACGTTCAACGTTCTCAAGTGACGAACCGAGCTGGGCAAGTGGTATTACTG
ATGAAGCGGCGTTAAAGAAAGCAGCGATGCAGTCTTTGATTACAGCAGGTGATAAAC
CAACACCCGTTAAGATCGTACAGCTAATCAAACCAATCCAAGCTAATCGTGAAATTG
CGCAAACCTTGTCTGCAATTACCGCTGCTGGTGGCCAAGCTGAATATGTTTCTGCAG
ATGTAAGTAAATGCAGCAAGCGTACAAATGGCAGTCGCTCCAGCTATCGCTAAGTTCG
GTGCAATCACTGGCATCATTTCATGGCGCGGGTGTGTTAGCTGACCAATTCATTGAGC
AAAAACACTGAGTGATTTTGTAGTCTGTTTACAGCACTAAAATTGACGGTTTGTAT
CGCTACTATCAGTCACTGAAGCAAGCAACATCAAGCAATTGGTATTGTTCTCGTCAG
CGGCTGGTTTCTACGGTAACCCCGGCCAGTCTGATTACTCGATTGCCAATGAGATCT
TAAATAAAACCGCATACCGCTTTAAATCATTGCACCCACAAGCTCAAGTATTGAGCT
TTAACTGGGGTCCTTGGGACGGTGGCATGGTAACGCCTGAGCTTAAACGTATGTTTG
ACCAACGTGGTGTTTACATTATTCCACTTGATGCAGGTGCACAGTTATTGCTGAATG
AACTAGCCGCTAATGATAACCGTTGTCCACAAATCCTCGTGGGTAATGACTTATCTA
AAGATGCTAGCTCTGATCAAAAGTCTGATGAAAAGAGTACTGCTGTAAAAAAGCCAC
AAGTTAGTCGTTTATCAGATGCTTTAGTAACTAAAAGTATCAAAGCGACTAACAGTA

FIG. 6-5

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GCTCTTTATCAAACAAGACTAGTGCTTTATCAGACAGTAGTGCTTTTCAGGTTAACG
AAAACCACTTTTTAGCTGACCACATGATCAAAGGCAATCAGGTATTACCAACGGTAT
GCGCGATTGCTTGGATGAGTGATGCAGCAAAGCGACTTATAGTAACCGAGACTGTG
CATTGAAGTATGTCGGTTTCGAAGACTATAAATTGTTTAAAGGTGTGGTTTTTGATG
GCAATGAGGCGGCGGATTACCAAATCCAATTGTCGCCTGTGACAAGGGCGTCAGAAC
AGGATTCTGAAGTCCGTATTGCCGCAAAGATCTTTAGCCTGAAAAGTGACGGTAAAC
CTGTGTTTTATTATGCAGCGACAATATTGTTAGCAACTCAGCCACTTAATGCTGTGA
AGGTAGAACTTCCGACATTGACAGAAAGTGTTGATAGCAACAATAAAGTAACTGATG
AAGCACAAGCGTTATACAGCAATGGCACCTTGTTCCACGGTGAAAGTCTGCAGGGCA
TTAAGCAGATATTAAGTTGTGACGACAAGGGCCTGCTATTGGCTTGTCAGATAACCG
ATGTTGCAACAGCTAAGCAGGGATCCTTCCCGTTAGCTGACAACAATATCTTTGCCA
ATGATTTGGTTTTATCAGGCTATGTTGGTCTGGGTGCGCAAACAATTTGGTTTAGGTA
GCTTACCTTCGGTGACAACGGCTTGGACTGTGTATCGTGAAGTGGTTGTAGATGAAG
TATTTTATCTGCAACTTAATGTTGTTGAGCATGATCTATTGGGTTACGCGGCAGTA
AAGCCCGTTGTGATATTCAATTGATTGCTGCTGATATGCAATTACTTGCCGAAGTGA
AATCAGCGCAAGTCAGTGTGAGTGACATTTTGAACGATATGTCATGATCGAGTAAAT
AATAACGATAGGCGTCATGGTGAGCATGGCGTCTGCTTTCTTCATTTTTTAACATTA
ACAATATTAATAGCTAAACGCGGTTGCTTTAAACCAAGTAAACAAGTGCTTTTAGCT
ATTACTATTCCAAACAGGATATTAAAGAGAATATGACGGAATTAGCTGTTATTGGTA
TGGATGCTAAATTTAGCGGACAAGACAATATTGACCGTGTGGAACGCGCTTTCTATG
AAGGTGCTTATGTAGGTAATGTTAGCCGCGTTAGTACCGAATCTAATGTTATTAGCA
ATGGCGAAGAACAAGTTATTACTGCCATGACAGTTCTTAACTCTGTCAGTCTACTAG
CGCAAACGAATCAGTTAAATATAGCTGATATCGCGGTGTTGCTGATTGCTGATGTAA
AAAGTGCTGATGATCAGCTTGTTAGTCCAAATTGCATCAGCAATTGAAAACAGTGTG
CGAGTTGTGTTGTTATTGCTGATTTAGGCCAAGCATTAAATCAAGTAGCTGATTTAG

FIG. 6-6

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TTAATAACCAAGACTGTCCTGTGGCTGTAATTGGCATGAATAACTCGGTAAATTTAT
CTCGTCATGATCTTGAATCTGTAAGTCAACAATCAGCTTTGATGAAACCTTCAATG
GTTATAACAATGTAGCTGGGTTTCGCGAGTTTACTTATCGCTTCAACTGCGTTTGCCA
ATGCTAAGCAATGTTATATATACGCCAACATTAAGGGCTTCGCTCAATCGGGCGTAA
ATGCTCAATTTAACGTTGGAAACATTAGCGATACTGCAAAGACCGCATTCAGCAAG
CTAGCATAACTGCAGAGCAGGTTGGTTTGTAGAAAGTGTGAGCAGTCGCTGATTCGG
CAATCGCATTGTCTGAAAGCCAAGGTTTAATGTCTGCTTATCATCATACGCAAACCTT
TGCATACTGCATTAAGCAGTGCCCGTAGTGTGACTGGTGAAGGCGGGTGTTTTTCAC
AGGTGCGCAGGTTTATTGAAATGTGTAATTGGTTTACATCAACGTTATATTCCGGCGA
TTAAAGATTGGCAACAACCGAGTGACAATCAAATGTCACGGTGGCGGAATTCACCAT
TCTATATGCCTGTAGATGCTCGACCTTGGTTCCACATGCTGATGGCTCTGCACACA
TTGCCGCTTATAGTTGTGTGACTGCTGACAGCTATTGTCATATTCTTTTACAAGAAA
ACGTCTTACAAGAACTTGTTTTGAAAGAAACAGTCTTGCAAGATAATGACTTAACTG
AAAGCAAGCTTCAGACTCTTGAACAAAACAATCCAGTAGCTGATCTGCGCACTAATG
GTTACTTTGCATCGAGCGAGTTAGCATTAAATCATAGTACAAGGTAATGACGAAGCAC
AATTACGCTGTGAATTAGAACTATTACAGGGCAGTTAAGTACTACTGGCATAAGTA
CTATCAGTATTAAACAGATCGCAGCAGACTGTTATGCCCGTAATGATACTAACAAAG
CCTATAGCGCAGTGCTTATTGCCGAGACTGCTGAAGAGTTAAGCAAAGAAATAACCT
TGGCGTTTGCTGGTATCGCTAGCGTGTTTAATGAAGATGCTAAAGAATGGAAAACCC
CGAAGGGCAGTTATTTTACCGCGCAGCCTGCAAATAAACAGGCTGCTAACAGCACAC
AGAATGGTGTACCTTCATGTACCCAGGTATTGGTGCTACATATGTTGGTTTAGGGC
GTGATCTATTTTCATCTATTCCACAGATTTATCAGCCTGTAGCGGCTTTAGCCGATG
ACATTGGCGAAAGTCTAAAAGATACTTTACTTAAATCCACGCAGTATTAGTCGTCATA
GCTTTAAAGAACTCAAGCAGTTGGATCTGGACCTGCGCGGTAAGTTAGCCAATATCG
CTGAAGCCGGTGTGGGTTTTGCTTGTGTGTTTACCAAGGTATTTGAAGAAGTCTTTG
CCGTAAAGCTGACTTTGCTACAGGTTATAGCATGGGTGAAGTAAGCATGTATGCAG
CACTAGGCTGCTGGCAGCAACCGGGATTGATGAGTGCTCGCCTTGACACAATCGAATA

FIG. 6-7

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CCTTTAATCATCAACTTTGCGGCGAGTTAAGAACACTACGTCAGCATTGGGGCATGG
ATGATGTAGCTAACGGTACGTTTCGAGCAGATCTGGGAAACCTATAACCATTAAGGCAA
CGATTGAACAGGTCGAAATTGCCTCTGCAGATGAAGATCGTGTGTATTGCACCATTA
TCAATACACCTGATAGCTTGTGTAGCCGGTTATCCAGAAGCCTGTCAGCGAGTCA
TTAAGAATTTAGGTGTGCGTGCAATGGCATTGAATATGGCGAACGCAATTCACAGCG
CGCCAGCTTATGCCGAATACGATCATATGGTTGAGCTATACCATATGGATGTTACTC
CACGTATTAATACCAAGATGTATTCAAGCTCATGTTATTTACCGATTCCACAACGCA
GCAAAGCGATTTCCACAGTATTGCTAAATGTTTGTGTGATGTGGTGGATTTCCAC
GTTTGGTTAATACCTTACATGACAAAGGTGCGCGGGTATTCATTGAAATGGGTCCAG
GTCGTTTCGTTATGTAGCTGGGTAGATAAGATCTTAGTTAATGGCGATGGCGATAATA
AAAAGCAAAGCCAACATGTATCTGTTCTGTGAATGCCAAAGGCACCAGTGATGAAC
TTACTTATATTCGTGCGATTGCTAAGTTAATTAGTCATGGCGTGAATTTGAATTTAG
ATAGCTTGTTTAACGGGTCAATCCTGGTTAAAGCAGGCCATATAGCAAACACGAACA
AATAGTCAACATCGATATCTAGCGCTGGTGAGTTATACCTCATTAGTTGAAATATGG
ATTTAAAGAGAGTAATTATGGAAAATATTGCAGTAGTAGGTATTGCTAATTTGTTCC
CGGGCTCACAAGCACCGGATCAATTTGGCAGCAATTGCTTGAACAACAAGATTGCC
GCAGTAAGGCGACCGCTGTTCAAATGGGCGTTGATCCTGCTAAATATACCGCCAACA
AAGGTGACACAGATAAATTTTACTGTGTGCACGGCGGTTACATCAGTGATTTCAATT
TTGATGCTTCAGGTTATCAACTCGATAATGATTATTTAGCCGGTTTAGATGACCTTA
ATCAATGGGGGCTTTATGTTACGAAACAAGCCCTTACCGATGCGGGTTATTGGGGCA
GTACTGCACTAGAAAACCTGTGGTGTGATTTTAGGTAATTTGTCATTCCCAACTAAAT
CATCTAATCAGCTGTTTATGCCTTTGTATCATCAAGTTGTTGATAATGCCTTAAAGG
CGGTATTACATCCTGATTTTCAATTAACGCATTACACAGCACCGAAAAAACACATG
CTGACAATGCATTAGTAGCAGGTTATCCAGCTGCATTGATCGCGCAAGCGGCGGGTC
TTGGTGGTTCACATTTTGCCTGGATGCGGCTTGTGCTTCATCTTGTATAGCGTTA
AGTTAGCGTGTGATTACCTGCATACGGGTAAAGCCAACATGATGCTTGCTGGTGCGG

FIG. 6-8

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TATCTGCAGCAGATCCTATGTTCTGTAATATGGGTTTCTCGATATTCCAAGCTTACC
CAGCTAACAATGTACATGCCCCGTTTGACCAAAATTCACAAGGTCTATTTGCCGGTG
AAGGCGCGGGCATGATGGTATTGAAACGTCAAAGTGATGCAGTACGTGATGGTGATC
ATATTTACGCCATTATTAAAGGCGGCGCATTATCGAATGACGGTAAAGGCGAGTTTG
TATTAAGCCCGAACACCAAGGGCCAAGTATTAGTATATGAACGTGCTTATGCCGATG
CAGATGTTGACCCGAGTACAGTTGACTATATTGAATGTCATGCAACGGGCACACCTA
AGGGTGACAATGTTGAATTGCGTTTCGATGGAAACCTTTTTTCAGTCGCGTAAATAACA
AACCATTACTGGGCTCGGTTAAATCTAACCTTGGTCATTTGTAACTGCCGCTGGTA
TGCCTGGCATGACCAAAGCTATGTTAGCGCTAGGTAAAGGTCTTATTCCTGCAACGA
TTAACTTAAAGCAACCACTGCAATCTAAAAACGGTTACTTTACTGGCGAGCAAATGC
CAACGACGACTGTGTCTTGGCCAACAACCTCCGGGTGCCAAGGCAGATAAACCGCGTA
CCGCAGGTGTGAGCGTATTTGGTTTTGGTGGCAGCAACGCCCATTTGGTATTACAAC
AGCCAACGCAAACACTCGAGACTAATTTTAGTGTGCTAAACCACGTGAGCCTTTGG
CTATTATTGGTATGGACAGCCATTTTGGTAGTGCCAGTAATTTAGCGCAGTTCAAAA
CCTTATTAAATAATAATCAAAATACCTTCCGTGAATTACCAGAACAACGCTGGAAAG
GCATGGAAAGTAACGCTAACGTCATGCAGTCGTTACAATTACGCAAAGCGCCTAAAG
GCAGTTACGTTGAACAGCTAGATATTGATTTCTTGCGTTTTAAAGTACCGCCTAATG
AAAAAGATTGCTTGATCCCGCAACAGTTAATGATGATGCAAGTGGCAGACAATGCTG
CGAAAGACGGAGGTCTAGTTGAAGGTCGTAATGTTGCGGTATTAGTAGCGATGGGCA
TGGAACCTGGAATTACATCAGTATCGTGGTCGCGTTAATCTAACCACCCAAATTGAAG
ACAGCTTATTACAGCAAGGTATTAACCTGACTGTTGAGCAACGTGAAGAACTGACCA
ATATTGCTAAAGACGGTGTTGCCTCGGCTGCACAGCTAAATCAGTATACGAGTTTCA
TTGGTAATATTATGGCGTCACGATTTTCGGCGTTATGGGATTTTTCTGGTCCTGCTA
TTACCGTATCGGCTGAAGAAAACCTCTGTTTATCGTTGTGTTGAATTAGCTGAAAATC
TATTTCAAACCAGTGATGTTGAAGCCGTTATTATTGCTGCTGTTGATTTGTCTGGTT
CAATTGAAAACATTACTTTACGTCAGCACTACGGTCCAGTTAATGAAAAGGGATCTG

FIG. 6-9

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TAAGTGAATGTGGTCCGGTTAATGAAAGCAGTTCAGTAACCAACAATATTCTTGATC
AGCAACAATGGCTGGTGGGTGAAGGCGCAGCGGCTATTGTGCTTAAACCGTCATCGC
AAGTCACTGCTGAGCAAGTTTATGCGCGTATTGATGCGGTGAGTTTTGCCCTGGTA
GCAATGCGAAAGCAATTACGATTGCAGCGGATAAAGCATTAACTTGCTGGTATCA
GTGCTGCTGATGTAGCTAGTGTTGAAGCACATGCAAGTGGTTTTAGTGCCGAAAATA
ATGCTGAAAAAACCGCGTTACCGACTTTATACCCAAGCGCAAGTATCAGTTCGGTGA
AAGCCAATATTGGTCATACGTTTAAATGCCTCGGGTATGGCGAGTATTATTAAACGG
CGCTGCTGTTAGATCAGAATACGAGTCAAGATCAGAAAAGCAAACATATTGCTATTA
ACGGTCTAGGTTCGTGATAACAGCTGCGCGCATCTTATCTTATCGAGTTCAGCGCAAG
CGCATCAAGTTGCACCAGCGCCTGTATCTGGTATGGCCAAGCAACGCCCACAGTTAG
TTAAAACCATCAAACCTCGGTGGTCAGTTAATTAGCAACGCGATTGTTAACAGTGCGA
GTTTCATCTTTACACGCTATTAAAGCGCAGTTTGCCGGTAAGCACTTAAACAAAGTTA
ACCAGCCAGTGATGATGGATAACCTGAAGCCCCAAGGTATTAGCGCTCATGCAACCA
ATGAGTATGTGGTGAAGTGGAGCTGCTAACACTCAAGCTTCTAACATTCAAGCATCTC
ATGTTCAAGCGTCAAGTCATGCACAAGAGATAGCACCAAACCAAGTTCAAAATATGC
AAGCTACAGCAGCCGCTGTAAGTTCACCCCTTTCTCAACATCAACACACAGCGCAGC
CCGTAGCGGCACCGAGCGTTGTTGGAGTGACTGTGAAACATAAAGCAAGTAACCAA
TTCATCAGCAAGCGTCTACGCATAAAGCATTTTTAGAAAGTCGTTTAGCTGCACAGA
AAAACCTATCGCAACTTGTTGAATTGCAAACCAAGCTGTCAATCCAACTGGTAGTG
ACAATACATCTAACAATACTGCGTCAACAAGCAATACAGTGCTAACAAATCCTGTAT
CAGCAACGCCATTAACTTGTGTCTAATGCGCCTGTAGTAGCGACAAACCTAACCA
GTACAGAAGCAAAAGCGCAAGCAGCTGCTACACAAGCTGGTTTTTCAGATAAAAGGAC
CTGTTGGTTACAACCTATCCACCGCTGCAGTTAATTGAACGTTATAATAAACCAGAAA
ACGTGATTTACGATCAAGCTGATTTGGTTGAATTCGCTGAAGGTGATATTGGTAAGG
TATTTGGTGCTGAATACAATATTATTGATGGCTATTCGCGTCGTGTACGTCTGCCAA
CCTCAGATTACTTGTTAGTAACACGTGTTACTGAACTTGATGCCAAGGTGCATGAAT

FIG. 6-10

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ACAAGAAATCATACATGTGTACTGAATATGATGTGCCTGTTGATGCACCGTTCTTAA
TTGATGGTCAGATCCCTTGGTCTGTTGCCGTGAATCAGGCCAGTGTGATTTGATGT
TGATTTTCATATATCGGTATTGATTTCCAAGCGAAAGGCGAACGTGTTTACCGTTTAC
TTGATTGTGAATTAACCTTTCCTTGAAGAGATGGCTTTTGGTGGCGATACTTTACGTT
ACGAGATCCACATTGATTTCGTATGCACGTAACGGCGAGCAATTATTATTCTTCTTCC
ATTACGATTGTTACGTAGGGGATAAGAAGGTACTTATCATGCGTAATGGTTGTGCTG
GTTTCTTTACTGACGAAGAACTTCTGATGGTAAAGGCGTTATTCATAACGACAAAG
ACAAAGCTGAGTTTAGCAATGCTGTTAAATCATCATTACGCCGTTATTACAACATA
ACCGTGGTCAATACGATTATAACGACATGATGAAGTTGGTTAATGGTGATGTTGCCA
GTTGTTTTGGTCCGCAATATGATCAAGGTGGCCGTAATCCATCATTGAAATTCTCGT
CTGAGAAGTTCCTTGATGATTGAACGTATTACCAAGATAGACCCAACCGGTGGTCATT
GGGGACTAGGCCTGTTAGAAGGTCAGAAAGATTTAGACCCTGAGCATTGGTATTTCC
CTTGTCACTTTAAAGGTGATCAAGTAATGGCTGGTTCGTTGATGTGCGAAGGTTGTG
GCCAAATGGCGATGTTCTTCATGCTGTCTCTTGGTATGCATACCAATGTGAACAACG
CTCGTTTCCAACCACTACCAGGTGAATCACAAACGGTACGTTGTCTGTTGGGCAAGTAC
TGCCACAGCGCAATACCTTAACTTACCGTATGGAAGTTACTGCGATGGGTATGCATC
CACAGCCATTTCATGAAAGCTAATATTGATATTTTGCTTGACGGTAAAGTGGTTGTTG
ATTTCAAAAACCTTGAGCGTGATGATCAGCGAACAAGATGAGCATTTCAGATTACCCTG
TAACACTGCCGAGTAATGTGGCGCTTAAAGCGATTACTGCACCTGTTGCGTCAGTAG
CACCAGCATCTTCACCCGCTAACAGCGCGGATCTAGACGAACGTGGTGTGAACCGT
TTAAGTTTCCTGAACGTCCGTTAATGCGTGTTGAGTCAGACTTGTCTGCACCGAAAA
GCAAAGGTGTGACACCGATTAAAGCATTTTGAAGCGCCTGCTGTTGCTGGTCATCATA
GAGTGCCTAACCAAGCACCGTTTACACCTTGGCATATGTTTGAGTTTTCGACGGGTA
ATATTTCTAACTGTTTCGGTCCTGATTTTGATGTTTATGAAGGTCGTATTCACCTC
GTACACCTTGTGGCGATTTACAAGTTGTTACTCAGGTTGTAGAAGTGCAGGGCGAAC
GTCTTGATCTTAAAAATCCATCAAGCTGTGTAGCTGAATACTATGTACCGGAAGACG

FIG. 6-11

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CTTGGTACTTTACTAAAAACAGCCATGAAACTGGATGCCTTATTCATTAATCATGG
AAATTGCATTGCAACCAAATGGCTTTATTTCTGGTTACATGGGCACGACGCTTAAAT
ACCCTGAAAAAGATCTGTTCTTCCGTAACCTTGATGGTAGCGGCACGTTATTAAAGC
AGATTGATTTACGCGGCAAGACCATTGTGAATAAATCAGTCTTGGTTAGTACGGCTA
TTGCTGGTGGCGCGATTATTCAAAGTTTCACGTTTGATATGTCTGTAGATGGCGAGC
TATTTTATACTGGTAAAGCTGTATTTGGTTACTTTAGTGGTGAATCACTGACTAACC
AACTGGGCATTGATAACGGTAAAACGACTAATGCGTGGTTTGTGATAACAATACCC
CCGCAGCGAATATTGATGTGTTTGATTAACTAATCAGTCATTGGCTCTGTATAAAG
CGCCTGTGGATAAACCGCATTATAAATTGGCTGGTGGTCAGATGAACTTTATCGATA
CAGTGTCACTGGTTGAAGGCGGTGGTAAAGCGGGCGTGGCTTATGTTTATGGCGAAC
GTACGATTGATGCTGATGATTGGTTCTTCCGTTATCACTTCCACCAAGATCCGGTGA
TGCCAGGTTTATTAGGTGTTGAAGCTATTATTGAGTTGATGCAGACCTATGCGCTTA
A-~~AA~~ATGATTTGGGTGGCAAGTTTGCTAACCACGTTTCATTGCGCCGATGACGCAAG
TTGATTGGAAATACCGTGGGCAAATTACGCCGCTGAATAAACAGATGTCACCTGGACG
TGCATATCACTGAGATCGTGAATGACGCTGGTGAAGTGCGAATCGTTGGTGATGCGA
ATCTGTCTAAAGATGGTCTGCGTATTTATGAAGTTAAAAACATCGTTTTAAGTATTG
TTGAAGCGTAAAGGGTCAAGTGTAACGTGCTTAAGCGCCGCATTGGTTAAAGACGCT
TTGCACGCCGTGAATCCGTCCATGGAGGCTTGGGGTTGGCATCCATGCCAACAACAG
CAAGCTTACTTTAATCAATACGGCTTGGTGTCCATTTAGACGCCTCGAACTTAGTAG
TTAATAGACAAAATAATTTAGCTGTGGAATGAATATAGTAAGTAATCATTTCGGCAGC
TACAAAAAAGGAATTAAGAATGTCGAGTTTAGGTTTTACAATAACAACGCAATTAA
CTGGGCTTGGAAGTAGATCCAGCGTCAGTTCATACACAAGATGCAGAAATTAAAGC
AGCTTTAATGGATCTAACTAAACCTCTCTATGTGGCGAATAATTCAAGGCGTAACTGG
TATAGCTAATCATACGTCAGTAGCAGGTGCGATCAGCAATAACATCGATGTTGATGT
ATTGGCGTTTTCGCAAAAGTTAAACCCAGAAGATCTGGGTGATGATGCTTACAAGAA
ACAGCACGGCGTTAAATATGCTTATCATGGCGGTGCGATGGCAAATGGTATTGCCTC

FIG. 6-12

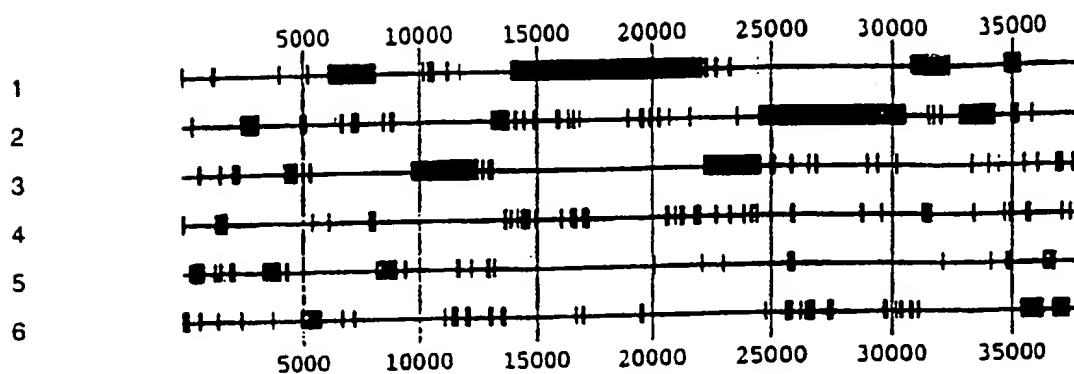
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GGTTGAATTGGTTGTTGCGTTAGGTAAAGCAGGGCTGTTATGTTTCATTTGGTGCTGC
AGGTCTAGTGCCTGATGCGGTTGAAGATGCAATTCGTCGTATTCAAGCTGAATTACC
AAATGGCCCTTATGCGGTTAACTTGATCCATGCACCAGCAGAAGAAGCATTAGAGCG
TGGCGCGGTTGAACGTTTCCTAAACTTGGCGTCAAGACGGTAGAGGCTTCAGCTTA
CCTTGGTTTAACTGAACACATTGTTTGGTATCGTGCTGCTGGTCTAACTAAAAACGC
AGATGGCAGTGTTAATATCGGTAACAAGGTTATCGCTAAAGTATCGCGTACCGAAGT
TGGTCGCCGCTTTATGGAACCTGCACCGCAAAAATTACTGGATAAGTTATTAGAACA
AAATAAGATCACCCCTGAACAAGCTGCTTTAGCGTTGCTTGTACCTATGGCTGATGA
TATTACTGGGGAAGCGGATTCTGGTGGTCATACAGATAACCGTCCGTTTTTAACATT
ATTACCGACGATTATTGGTCTGCGTGATGAAGTGCAAGCGAAGTATAACTTCTCTCC
TGCATTACGTGTTGGTGCTGGTGGTGGTATCGGAACGCCTGAAGCAGCACTCGCTGC
ATTTAACATGGGCGCGGCTTATATCGTTCCTGGGTTCTGTGAATCAGGCGTGTTGA
AGCGGGTGCACTCTGAATATACTCGTAACTGTTATCGACAGTTGAAATGGCTGATGT
GACTATGGCACCTGCTGCAGATATGTTTGAAATGGGTGTGAAGCTGCAAGTATTAAA
ACGCGGTTCTATGTTGCGGATGCGTGCGAAGAACTGTATGACTTGTATGTGGCTTA
TGACTCGATTGAAGATATCCCAGCTGCTGAACGTGAGAAGATTGAAAAACAAATCTT
CCGTGCAAAACCTAGACGAGATTTGGGATGGCACTATCGCTTCTTTACTGAACGCGA
TCCAGAAATGCTAGCCCGTGCAACGAGTAGTCCTAAACGTAAAATGGCACTTATCTT
CCGTGTTGTTATCTTGGCCTTTCTTCACGCTGGTCAAACACAGGCGAGAAGGGACGTGA
AATGGATTATCAGATTTGGGCAGGCCCAAGTTTAGGTGCATTCAACAGCTGGGTGAA
AGGTTCTTACCTTGAAGACTATACCCGCCGTGGCGCTGTAGATGTTGCTTTGCATAT
GCTTAAAGGTGCTGCGTATTTACAACGTGTAAACCAGTTGAAATTGCAAGGTGTTAG
CTTAAGTACAGAATTGGCAAGTTATCGTACGAGTGATTAATGTTACTTGATGATATG
TGAATTAATTAAAGCGCCTGAGGGCGCTTTTTTTGGTTTTTAACTCAGGTGTTGTAA
CTCGAAATTGCCCCTTTC

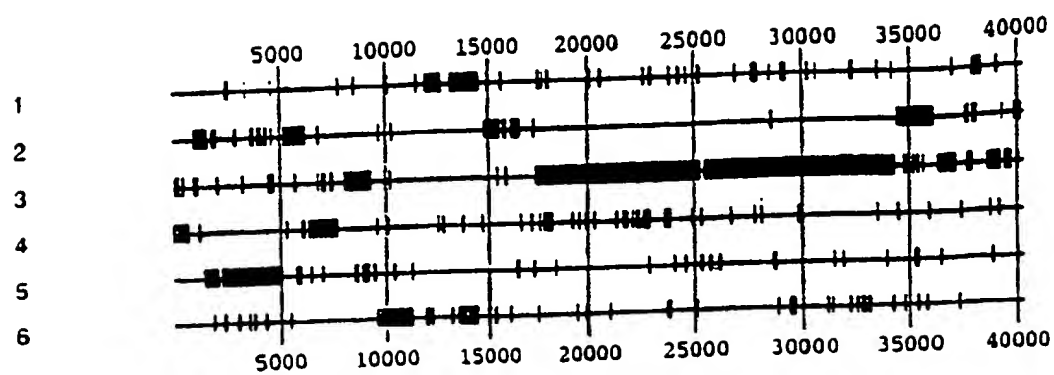
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FIG. 6-13

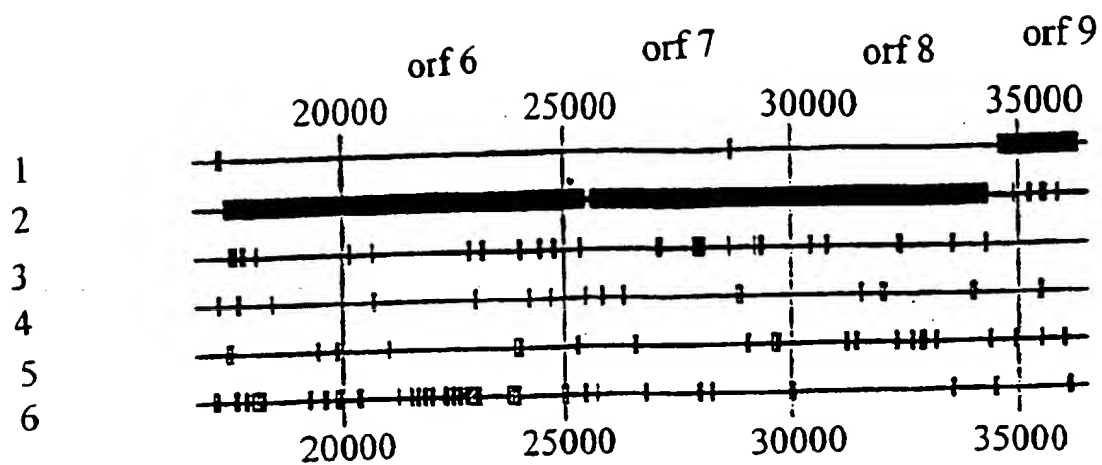
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**FIG. 7A**

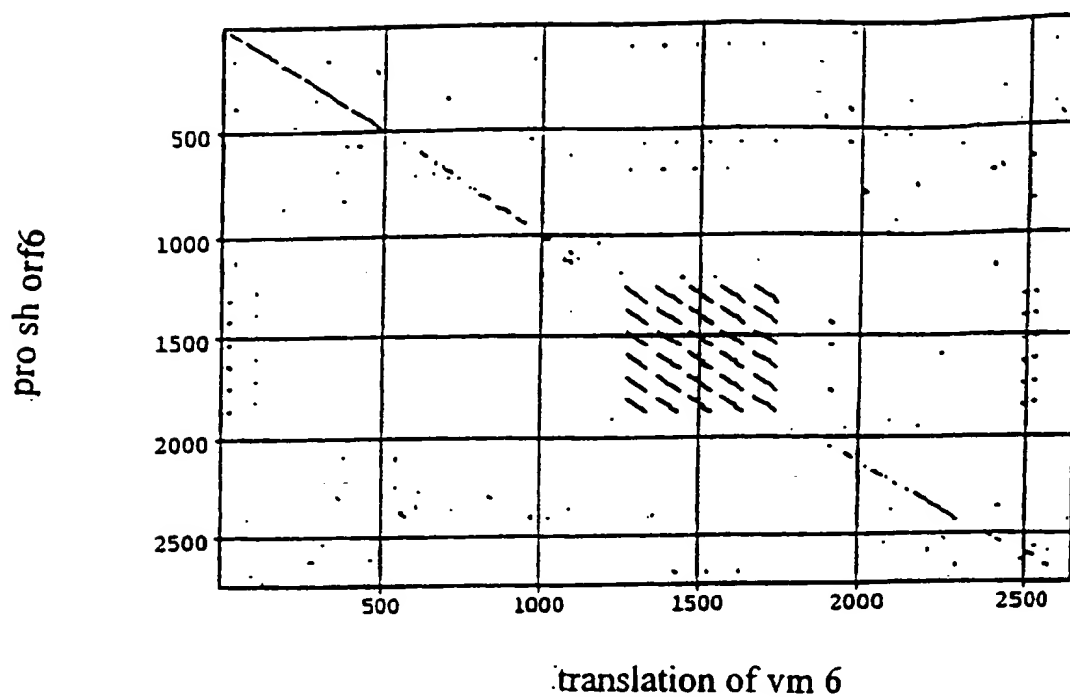
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**FIG. 7B**

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**FIG. 8**

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**FIG. 9**

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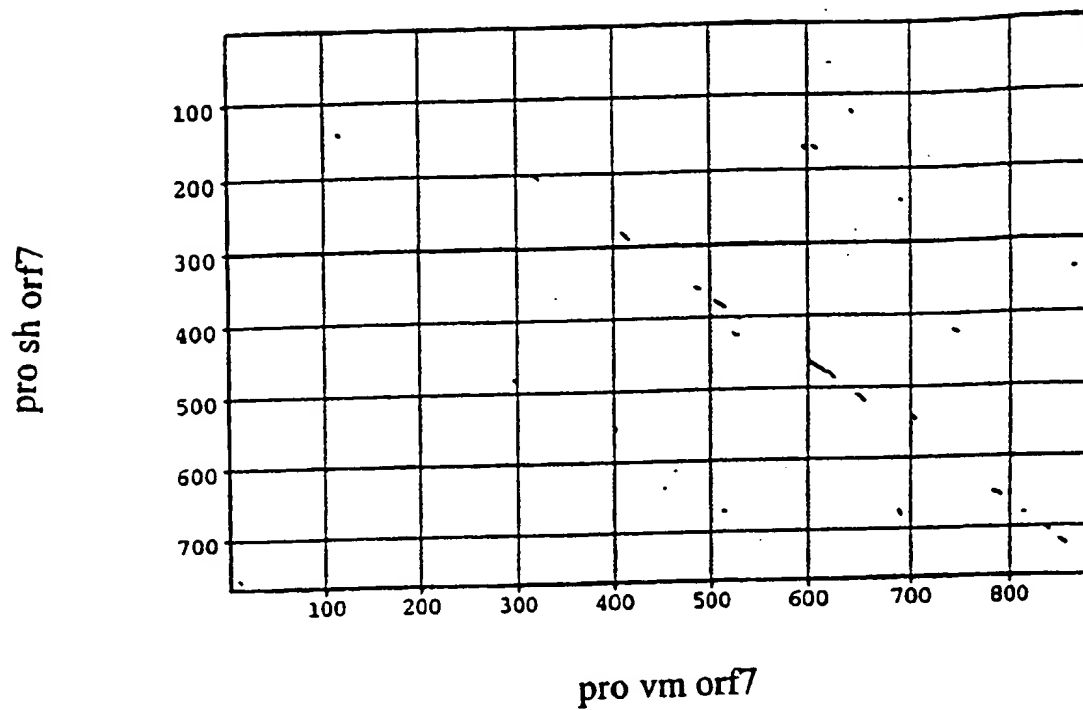


FIG. 10

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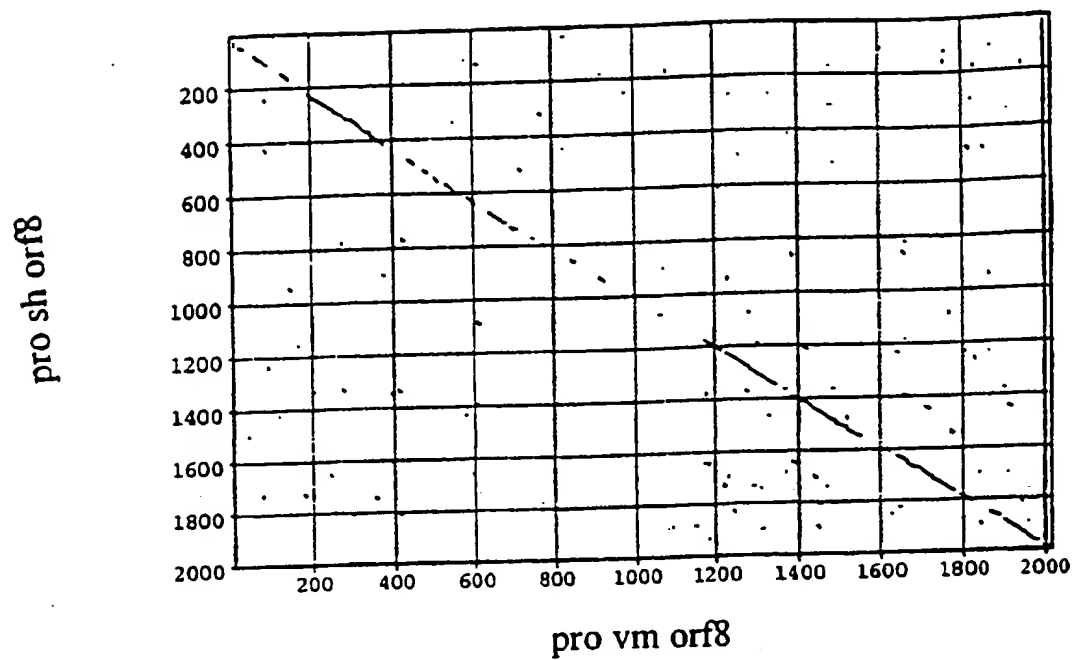
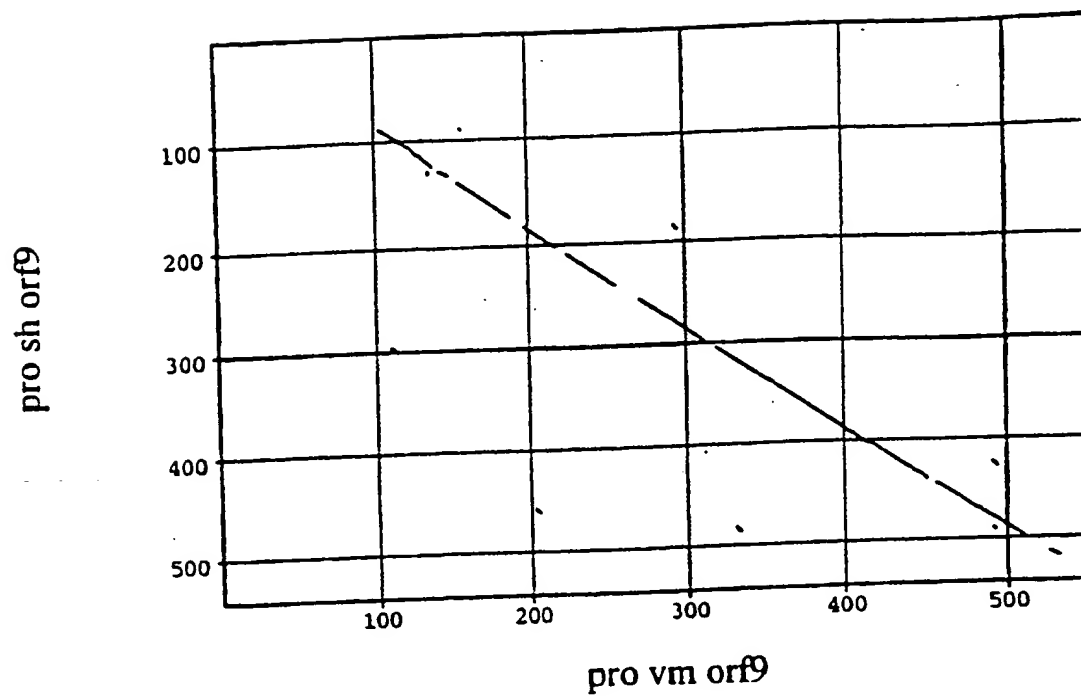
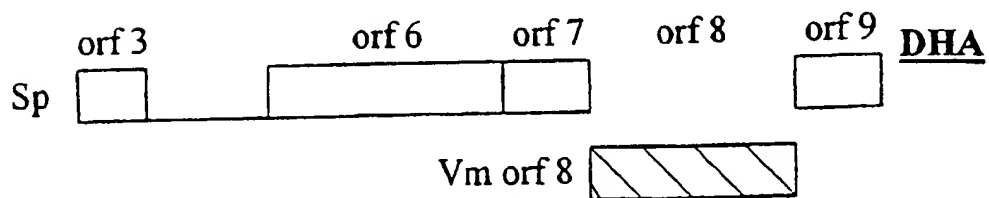
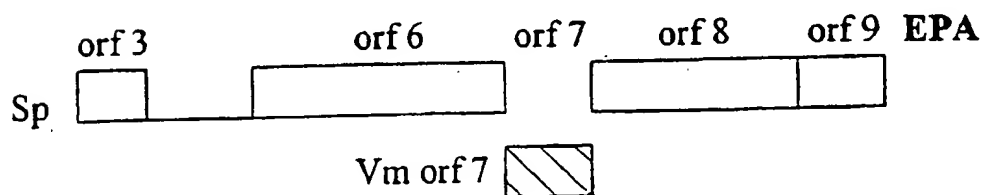
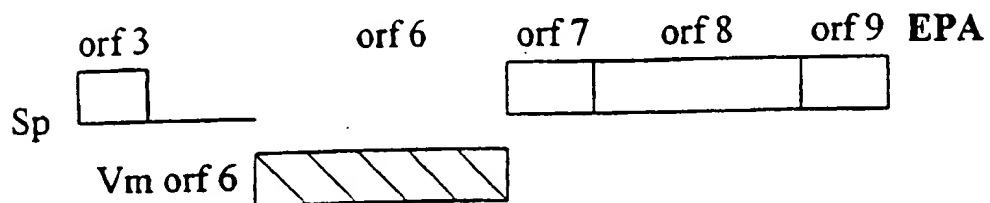
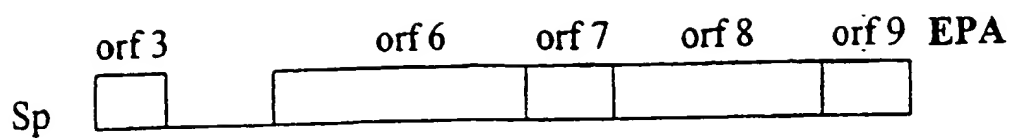


FIG. 11

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**FIG. 12**

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**FIG. 13**

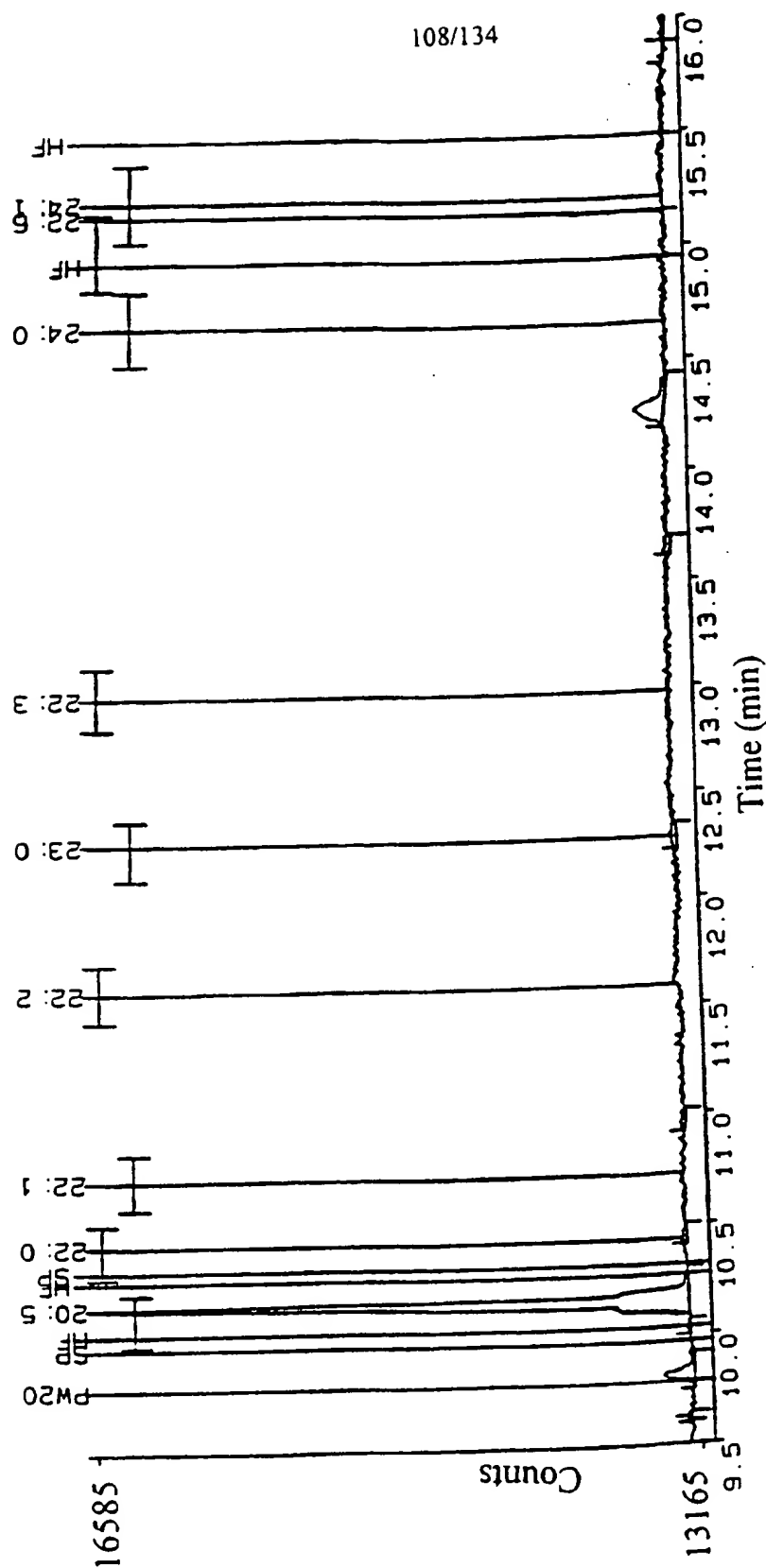
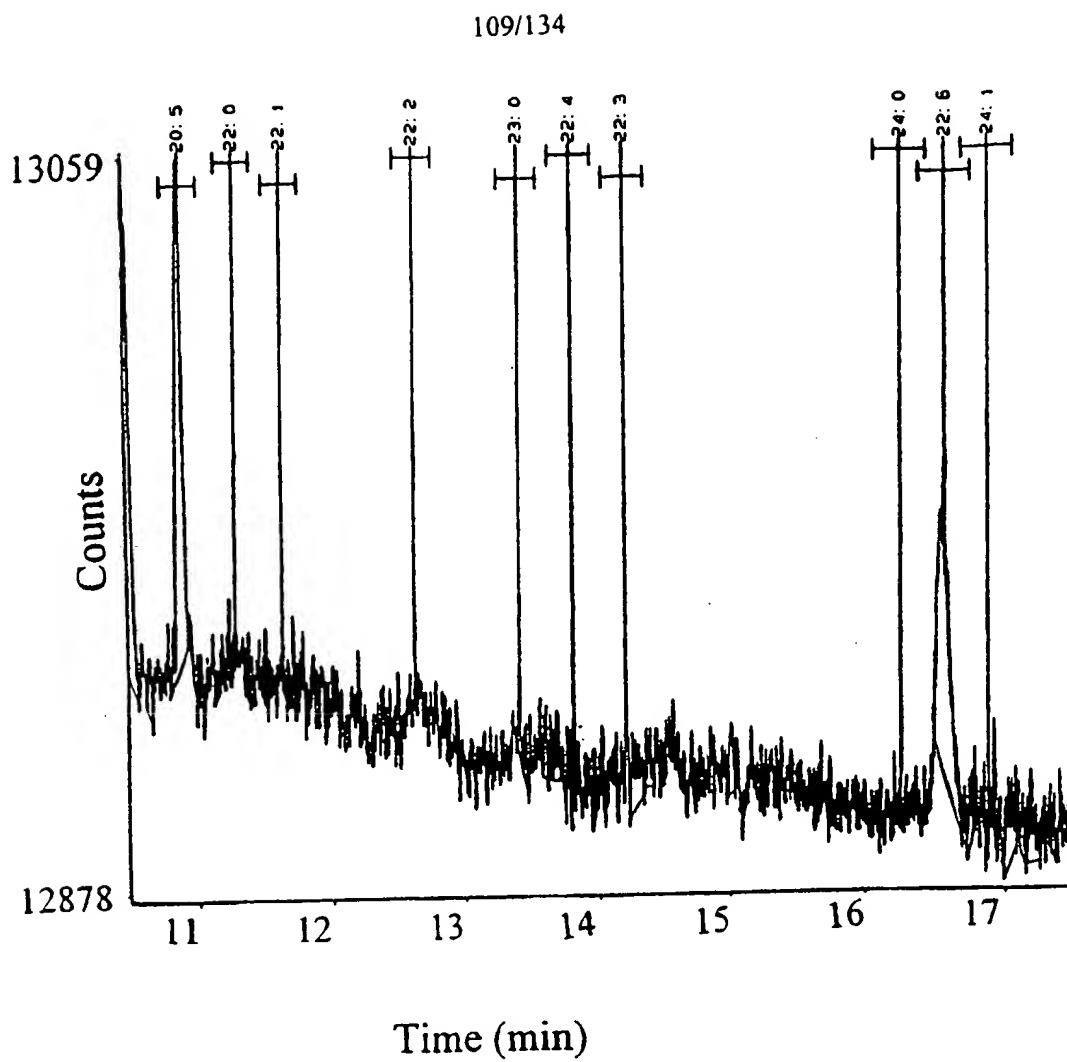


FIG. 14

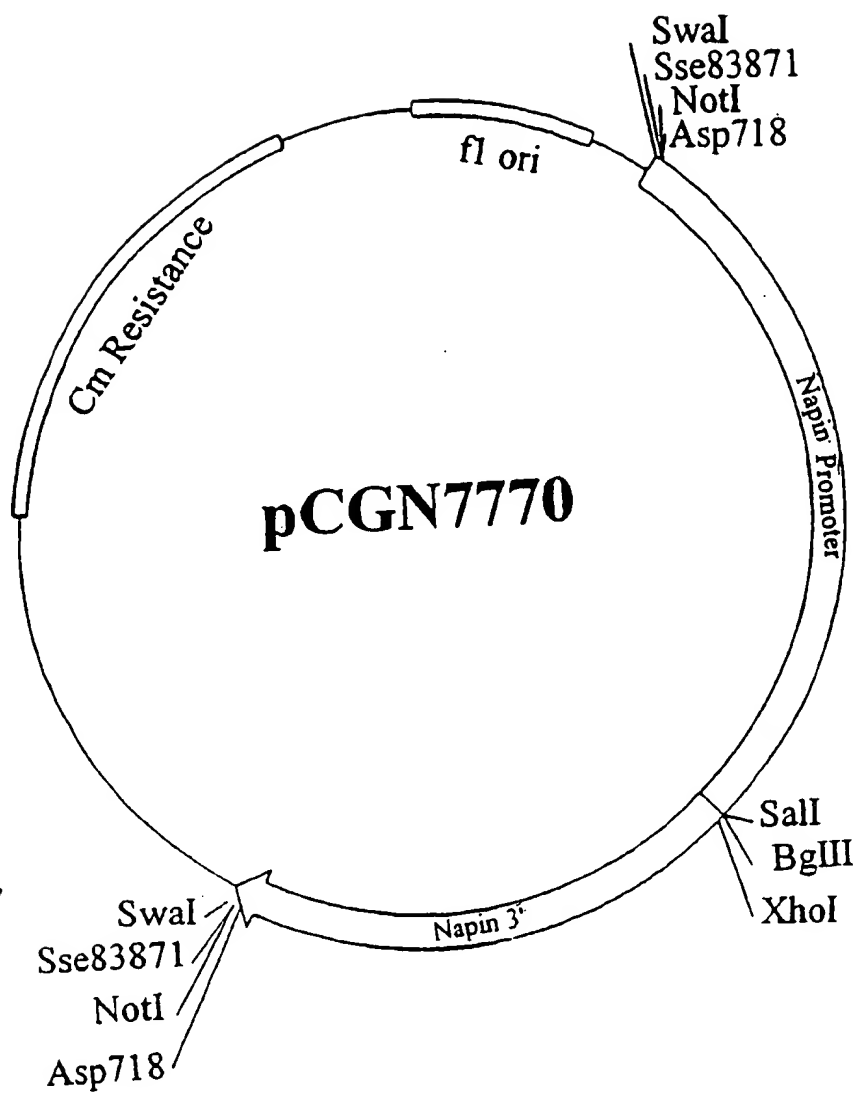
**FIG. 15**

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<u>EPA (%Fatty acids)</u>	<u>DHA (%Fatty acids)</u>	<u>20 deg C</u>
0.00	0.06	pEPAD8
0.60	0.70	4
0.64	0.66	5
0.33	0.22	6s
0.45	0.59	6l
		<u>23 deg C</u>
		pEPAD8
0.02	0.06	4
0.32	0.62	6s
0.27	0.22	6l
0.18	0.65	

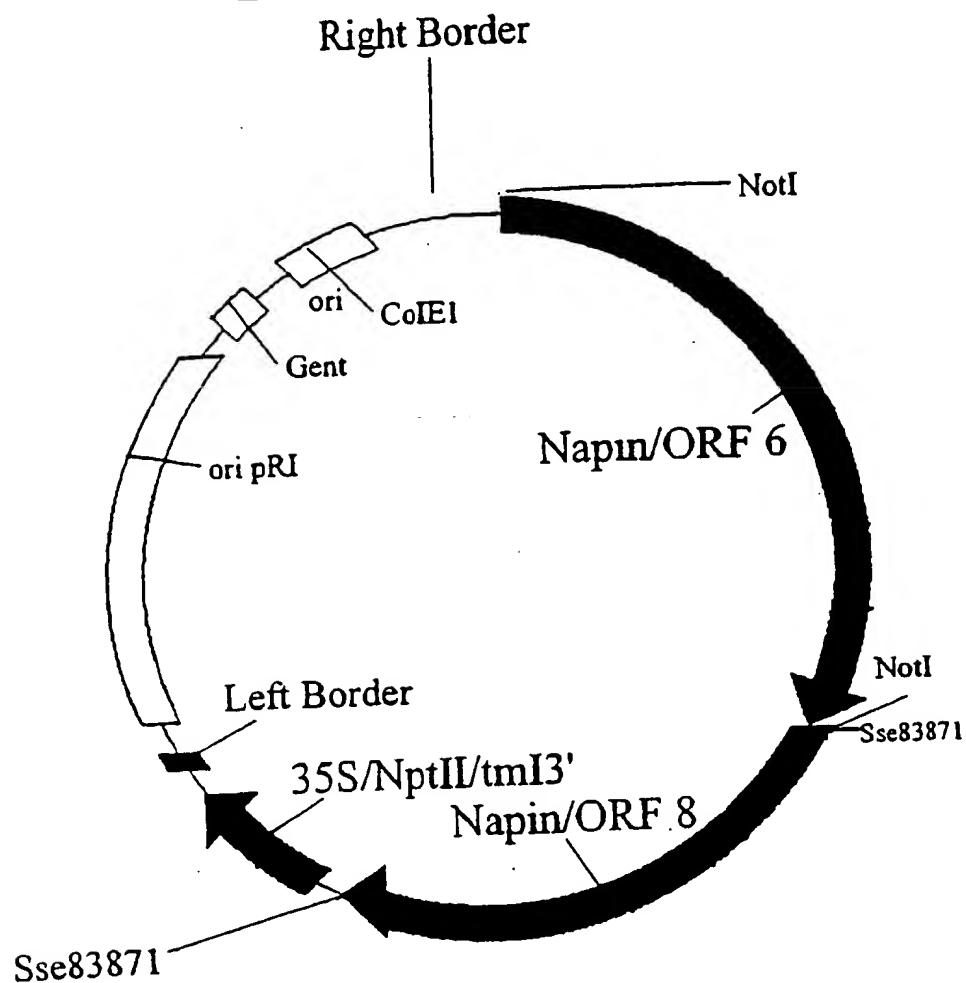
FIGURE 16

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**FIG. 17**

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pCGN8535

**FIG. 18**

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pCGN8537

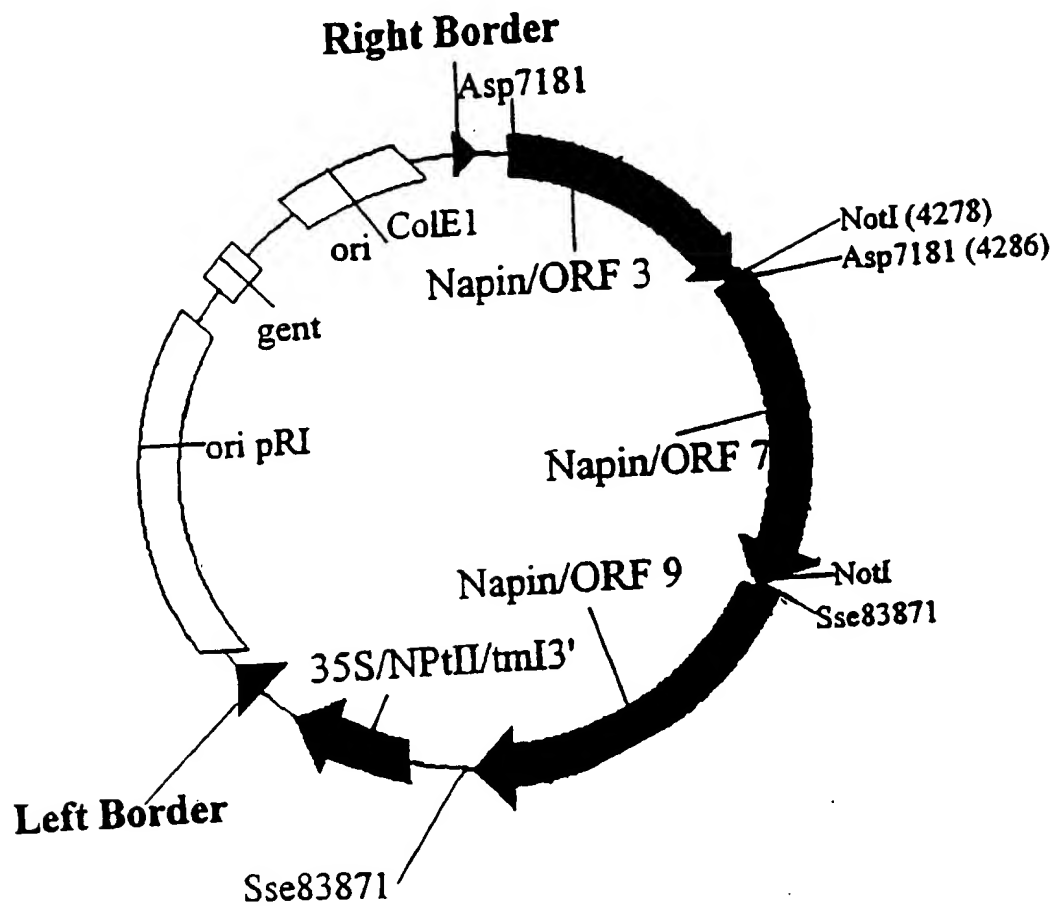


FIG. 19

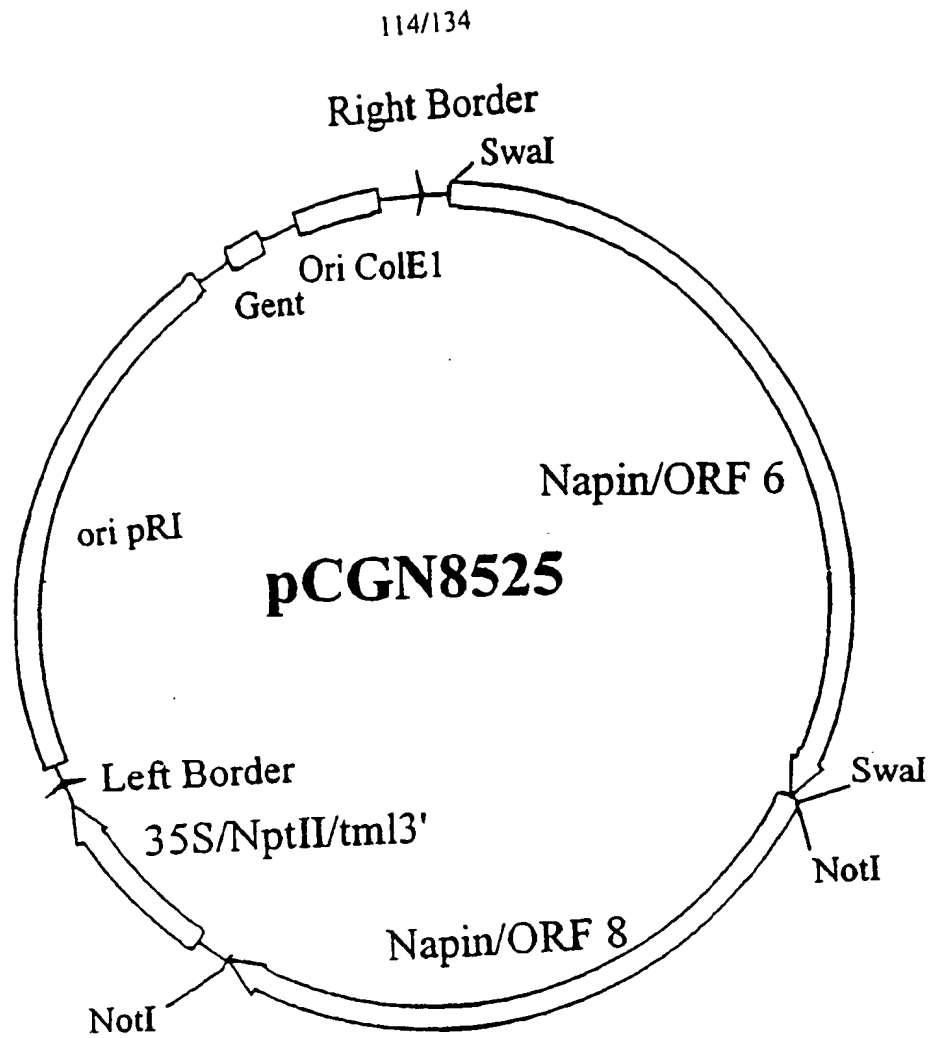
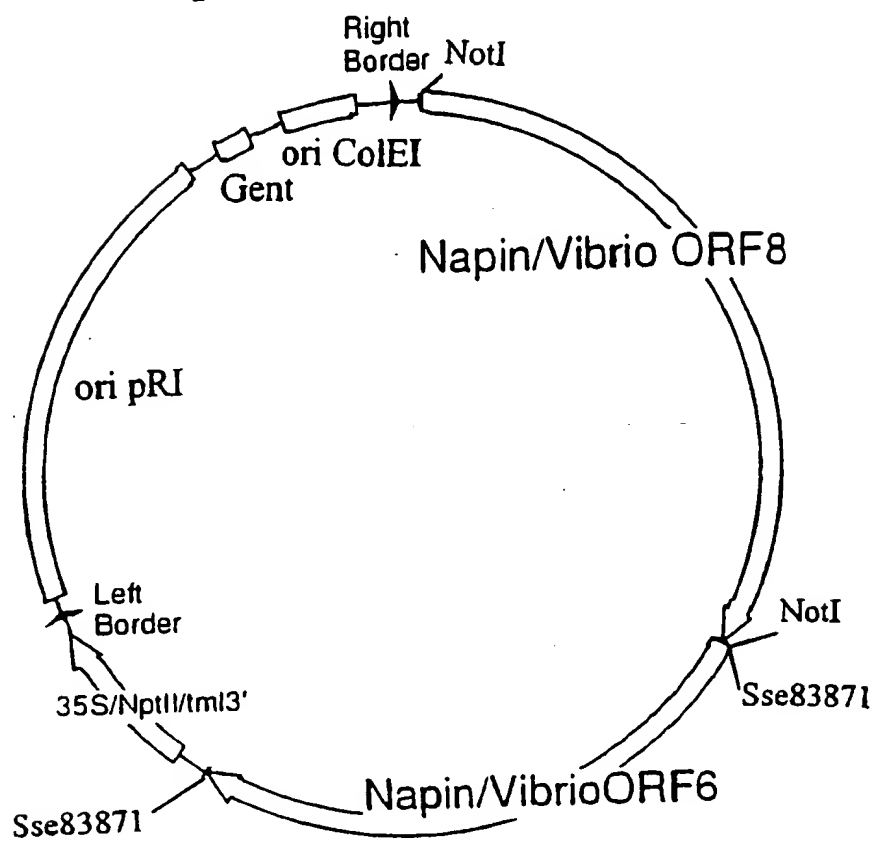


FIG. 20

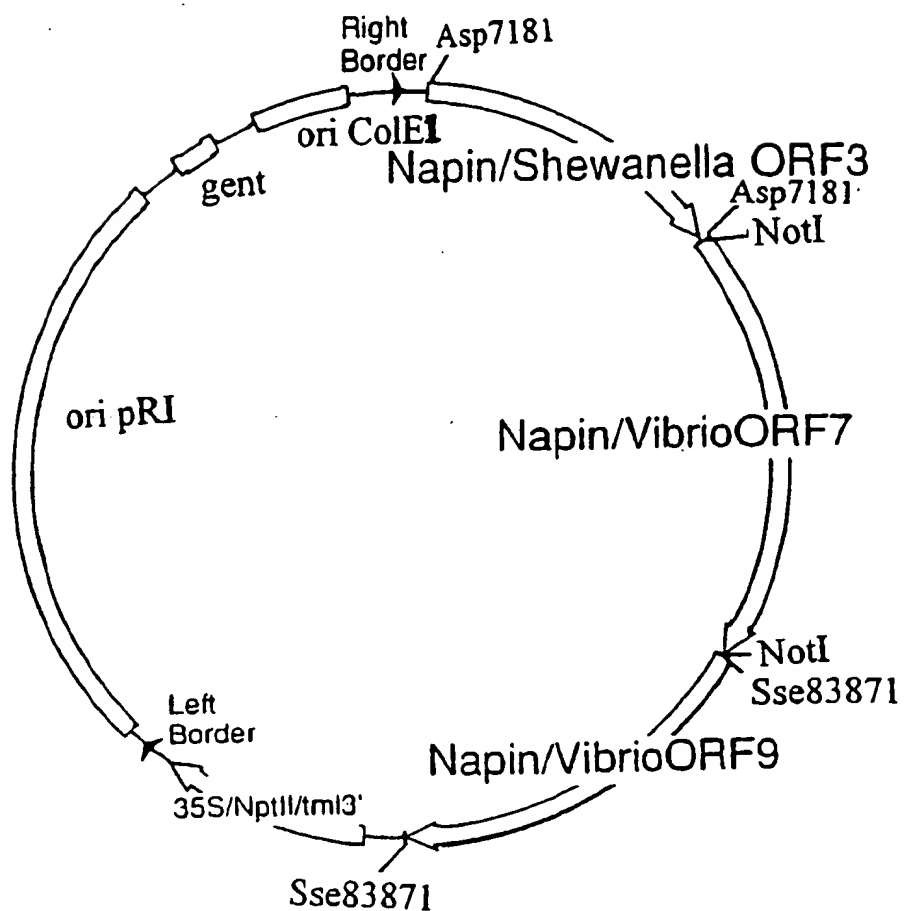
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pCGN8560

**FIG. 22**

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pCGN8556

**FIG. 23**

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↓
 ATT GGT AAA AAT AGG GGT TAT GTT TGT TGC TTT AAA GAG TGT CCT GAA
 I G K N R G Y V C C F K E C P E

 AAA ↓ 9157 ↓ ↓
 TTT CTA ACT TCT CGA TTG ATT TCC TTA TAC TTC TGT CCG TTA ACA
 K L L T S R L I S L Y F C P L T

 ATA CAA GAG TGC GAT AAC CAG ACT ACA GAG TTG GTT AAG TCA TGG CTG
 I Q E C D N Q T T E L V K S W L

 CCT GAA GAT GAG TTA ATT AAG GTT AAT CGC TAC ATT AAA CAA GAA GCT
 P E D E L I K V N R Y I K Q E A

 9016 ↓
 AAA ACT CAA GGT TTA ATG GTA AGA G
 K T Q G L M V R

FIG. 24

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```

AGCGAAATGC TTATCAAGAA ATTCCAAGAT CAATACATCA CTGGGAAGAA AATTCATTCC 60
CTGGTTCACT GGGTAACGTT ATTTCCGGCC GTATTGCTAA CCGCTTCGAC CTTGGTGGCA 120
TGAACGTGTG CGTTGATGCA GCATGTGCAG GCCCTCTTGC TGCATTGCGT ATGGCATTAA 180
GCGAGCTTGT TGAAGGCCGC AGCGAAATGA TGATTACAGG TGGTGTGTGT ACCGATAACT 240
CACCAACCAT GTACATGAGC TTCTCTAAAA CACCGGCATT CACGACAAAC GAAACAATTC 300
AACCATTCTGA TATTGACTCG AAAGGTATGA TGATTGGTGA AGGTATCGGT ATGATTGCGC 360
TTAAACGTCT TGAAGACGCA GAGCGTGATG GCGACCGTAT CTATTCCGTG ATTAAAGGTG 420
TTGGGTGCAT CTTCAGACGG TAATTATTA AGAGTANTTA TCGCNCNTCGT CCTGAAGGTC 480
AGGCTAAGGC ACTTAAACGT GCTTACGACG ATGCAGGTTT CGCACCCGCAC ACACCTGGCT 540
TACTTGAAGC CCACGGCACA GGCACAGCAG CAGGTGATGT GGCAGAATTC AGTGGTCTTA 600
ACTCTGTATT CAGTGAAGGC AATGACGAAA AGCAACACAT CGCATTAGGT TCAGTGAAT 660
CACAGATTGG TCACACTAAA TCAACAGCGG GTCATGCGGG TCTAATCAAA GCGTCTTTAG 720
CACTGCACCA TAAAGTACTG CCGCCCAACAA TCAATGTAAC CAGCCCCTAAC CCTAAACTGA 780
ATATTGAAGA CTCGCCTTTC TACCTCAATA CACAGACGCG TCCATGGATG CAACGTGTCTG 840
ATGGTACACC GCGTCGTGCT GGTATTAGCT CATTTGGTTT TGGTG 885

```

FIG. 25

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[illegible]

```

impl str +
          AGA ACGCAAAGTT GCGCACTGT TTGGTCGCCA
          | | | | | | | | | | | | | | | |
          CAA AGCGGGTGAT GCGCACTGT TTGGTCGCTT
3-2 (-VECTO

```

FIG. 26-1

3-2 (-VECTO GACCAAACAC TTTGGGCGCG CCAGTGATGA AAAGCAATAT ATCGCCTTAG GCTCAGTTAA

```

      jmp1 str +
      C ATGCGCTAG GTTCAGTTAA
      | | | | | | | | | |
      T ATCGCCTTAG GCTCAGTTAA

```

```

      jmpl str +
      AGGTTCAACA
      |||
      3-2(-VECTO GACCTAACAC

```

3-2 (-VECTO ATCGCAAATT GGTCACTACTA AATCTGCGGC TGGCTCTCGG GGTATGATTA AGCGGGCATT

```

      jmp1 str +
      CG GCTTCGATT TGGCGGCATG
      ||| | ||| | ||| |
      CG CGTATGATTA AGGCGGCATT
3-2(-VECTO

```

jmp1 str + ATCACAAATT GGTCACTACTA AATCAACTGC AGGT
 ||| ||||| ||||| ||| | || ||
 3-2(-VECTO ATCGCAAATT GGTCACTACTA AATCTGCGGC TGGC

FIG. 26-2

FIG. 26-3

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```

      CTCACCTT TGTATCTAAA CACTGAGACT TCGTCCATGG TTACCACGGTGT
      | | | | | | | | | | | | | | | | | | | | | | | | | | | |
      CAGCCCCG TATACCTAAA CAGCGAAACG GCGTCCTTGG ATGCCACGTGA

      jmp1 str +
      3-2(-VECTO

      380      400
      *      *
      AGATGGTATT CCACGTCGTG CAGGTATTAG CTCATTGGT TTTGGTGGC

      jmp1 str +
      3-2(-VECTO
      AGATGGTATT CCACGTCGTG CAGGTATTAG CTCATTGGT TTTGGTGGC
  
```

FIG. 26-4

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CGCTGCCGCCGCGTCTCGCCGCGCCGCGCCGCGCCGCGCCGCGCTCGCGCGCACGCC
CGCGCGTCTCGCCGCGCCTGCTGTCTCGAACGAGCTTCTCGAGAAGGCCGAGACCGTCCG
TCATGGAGGTCTCGCCGCCAAGACTGGCTACGAGACTGACATGATCGAGTCCGACATG
GAGCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTGAGATCCTCTCCGAGGT
TCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGACGCTCTCAGCCGCACTCGCACTG
TGGGTGAGGTGCTCAACGCCATGAAGGCTGAGATCGCTGGTGGCTCTGCCCCGGCGCCT
GCCGCCGCTGCCCCAGGTCCGGCTGCTGCCGCCCTGCGCCTGCTGTCTCGAGCGAGCT
TCTCGAGAAGGCCGAGACTGTCGTATGGAGGTCTCGCCGCCAAGACTGGCTACGAGA
CTGACATGATTGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAG
CGTGTGAGATTCTCTCCGAGGTTGAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGA
CGCTCTCAGCCGCACTCGCACTGTTGGTGAGGTGCTCGATGCCATGAAGGCTGAGATCG
CTGGCAGCTCCGCCTCGGCGCCTGCCGCCGCTGCTCCTGCTCCGGCTGCTGCCGCTCCT
GCGCCCGCTGCCGCCGCCCTGCTGTCTCGAACGAGCTTCTCGAGAAAGCCGAGACTGT
CGTCATGGAGGTCTCGCCGCCAAGACTGGCTACGAGACTGACATGATCGAGTCCGACA
TGGAGCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTGAGATCCTCTCCGAG
GTTGAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCCCTCAGCCGCACCCGCAC
TGTTGGCGAGGTTGTGATGCCATGAAGGCCGAGATCGCTGGTGGCTCTGCCCCGGCGC
CTGCCGCCGCTGCCCTGCTCCGGCTGCCGCCGCCCTGCTGTCTCGAACGAGCTTCTT
GAGAAGGCCGAGACTGTCGTATGGAGGTCTCGCCGCCAAGACTGGCTACGAGACCGA
CATGATCGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAGCGTG
TCGAGATTCTCTCCGAGGTTGAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCT
CTCAGCCGCACTCGCACTGTTGGCGAGGTGCTCGATGCCATGAAGGCTGAGATCGCCGG
CAGCTCCGCCCGCGCCTGCCGCCGCTGCTCCTGCTCCGGCTGCTGCCGCTCCTGCGC
CCGCTGCCGCTGCCCTGCTGTCTCGAGCGAGCTTCTCGAGAAGGCCGAGACCGTCTGTC
ATGGAGGTCTCGCCGCCAAGACTGGCTACGAGACTGACATGATTGAGTCCGACATGGA
GCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTGAGATCCTCTCCGAGGTTT
AGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCCCTCAGCCGCACCCGCACTGTT
GGCGAGGTTGTGATGCCATGAAGGCCGAGATCGCTGGTGGCTCTGCCCCGGCGCCTGC
CGCCGCTGCCCTGCTCCGGCTGCCGCCGCCCTGCTGTCTCGAACGAGCTTCTTGAGA
AGGCCGAGACCGTCTGTCATGGAGGTCTCGCCGCCAAGACTGGCTACGAGACCGACATG
ATCGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAGCGTGTGGA
GATTCTCTCCGAGGTTGAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGACGCTCTCA
GCCGCACTCGCACTGTTGGCGAGGTGCTCGATGCCATGAAGGCTGAGATCGCTGGTGGC
TCTGCCCGCGCGCCTGCCGCCGCTGCTCCTGCCTCGGCTGGCGCCGCGCCTGCGGTCAA
GATTGACTCGGTCCACGGCGCTGACTGTGATGATCTTCCCTGATGCACGCCAAGGTGG
TTGACATCCGCCGCCCGGACGAGCTCATCCTGGAGCGCCCCGAGAACCGCCCCGTTCTC
GTTGTGATGACGGCAGCGAGCTCACCTCGCCCTGGTCCGCGTCTCTCGGCGCCTGCGC
CGTTGTCTGACCTTTGAGGGTCTCCAGCTCGCTCAGCGCGCTGGTGCCGCTGCCATCC
GCCACGTGCTGCCAAGGATCTTCCGCGGAGAGCGCCGAGAAGGCCATCAAGGAGGCC
GAGCAGCGCTTTGGCGCTCTCGGCGGCTTCATCTCGCAGCAGGCGGAGCGCTTCGAGCC
CGCCGAAATCCTCGGCTTACGCTCATGTGCCCAAGTTCGCCAAGGCTTCCCTCTGCA
CGGCTGTGGCTGGCGGCCGCCCGGCTTTATCGGTGTGGCGCGCCTTGACGGCCGCTC

Figure 27 A-1

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GGATTCACTTCGCAGGGCACTTCTGACGCGCTCAAGCGTGCCCAGCGTGGTGCCATCTT
TGGCCTCTGCAAGACCATCGGCCTCGAGTGGTCCGAGTCTGACGTCTTTTCCCGCGGCG
TGGACATTGCTCAGGGCATGCACCCCGAGGATGCCGCGTGGCGATTGTGCGCGAGATG
GCGTGCGCTGACATTTCGCATTTCGCGAGGTTCGGCATTGGCGCAAACCAGCAGCGCTGCAC
GATCCGTGCCGCCAAGCTCGAGACCGGCAACCCGAGCGCCAGATCGCCAAGGACGACG
TGCTGCTCGTTTCTGGCGGCGCTCGCGGCATCACGCCTCTTTGCATCCGGGAGATCACG
CGCCAGATCGCGGGCGGCAAGTACATTCTGCTTGGCCGAGCAAGGTCTCTGCGAGCGA
ACCGGCATGGTGCGCTGGCATCACTGACGAGAAGGCTGTGCAAAAGGCTGCTACCCAGG
AGCTCAAGCGCGCCTTTAGCGCTGGCGAGGGCCCCAAGCCCACGCCCCGCGCTGTCACT
AAGCTTGTGGGCTCTGTTCTTGGCGCTCGCGAGGTGCGCAGCTCTATTGCTGCGATTGA
AGCGCTCGGCGGCAAGGCCATCTACTCGTCTGCGACGTGAACTCTGCCGCGGACGTGG
CCAAGGCCGTGCGCGATGCCGAGTCCCAGCTCGGTGCCGCGCTCTCGGGCATCGTTCAT
GCCTCGGGCGTGCTCCGCGACCGTCTCATCGAGAAGAAGCTCCCCGACGAGTTCGACGC
CGTCTTTGGCACCAAGGTCACCGGTCTCGAGAACCTCCTCGCCGCGCTCGACCGCGCCA
ACCTCAAGCACATGGTCCTCTTCAGCTCGCTCGCCGGCTTCACGGCAACGTTCGGCCAG
TCTGACTACGCCATGGCCAACGAGGCCCTTAACAAGATGGGCCTCGAGCTCGCCAAGGA
CGTCTCGGTCAAGTCGATCTGCTTCGGTCCCTGGGACGGTGGCATGGTGACGCCGCGAGC
TCAAGAAGCAGTTCAGGAGATGGGCGTGAGATCATCCCCCGAGGGCGGCGCTGAT
ACCGTGGCGCGCATCGTGCTCGGCTCCTCGCCGGCTGAGATCCTTGTCGGCAACTGGCG
CACCCCGTCCAAGAAGGTCGGCTCGGACACCATCACCTGCACCGCAAGATTTCCGCCA
AGTCCAACCCCTTCCTCGAGGACCACGTATCCAGGGCCGCGCGTGCTGCCCATGACG
CTGGCCATTGGCTCGCTCGCGGAGACCTGCCTCGGCCTCTTCCCCGGCTACTCGCTCTG
GGCCATTGACGACGCCAGCTCTTCAAGGGTGTCACTGTGACGGCGACGTCAACTGCG
AGGTGACCCTCACCCCGTCGACGGCGCCCTCGGGCCGCGTCAACGTCCAGGCCACGCTC
AAGACCTTTTCCAGCGGCAAGCTGGTCCC GGCTACCGCGCCGTATCGTGCTCTCCAA
CCAGGGCGCGCCCCCGGCCAACGCCACCATGCAGCCGCCCTCGCTCGATGCCGATCCGG
CGCTCCAGGGCTCCGTCTACGACGGCAAGACCCTCTTCCACGGCCCGGCTTCCGCGGC
ATCGATGACGTGCTCTCGTGACCAAGAGCCAGCTTGTGGCCAAGTGACGCGCTGTCCC
CGGCTCCGACGCCGCTCGCGGCGAGTTTGCCACGGACACTGACGCCCATGACCCCTTCG
TGAACGACCTGGCCTTTAGGCCATGCTCGTCTGGGTGCGCCGACGCTCGGCCAGGCT
GCGTCCCCAACTCGATCCAGCGCATCGTCCAGCACCGCCCGGTCCCGCAGGACAAGCC
CTTCTACATTACCCTCCGCTCCAACCAGTCGGGCGGTCACTCCAGCACAAAGCACGCCC
TTCAGTTCCACAACGAGCAGGGCGATCTCTTCATTGATGTCCAGGCTTCGGTCATCGCC
ACGGACAGCCTTGCCTTCTAA

Figure 27 A-2

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TGCCGTCTTTGAGGAGCATGACCCCTCCAACGCCGCCTGCACGGGCCACGACTCCATTT
CTGCGCTCTCGGCCCGCTGCGGCGGTGAAAGCAACATGCGCATCGCCATCACTGGTATG
GACGCCACCTTTGGCGCTCTCAAGGGACTCGACGCCTTCGAGCGCGCCATTTACACCGG
CGCTCACGGTGCCATCCCACTCCCAGAAAAGCGCTGGCGCTTTCTCGGCAAGGACAAGG
GAGGTGCACTTCCAGCGCCTCCGCACGCCCATGACCCCTGAAGACATGCTCCTCCCTCA
GCAGCTTCTGGCCGTCACCACCATTGACCGCGCCATCCTCGACTCGGGAATGAAAAAGG
GTGGCAATGTCGCCGTCTTTGTGCGCCTCGGCACCGACCTCGAGCTCTACCGTCA'CGT
GCTCGCGTCGCTCTCAAGGAGCGCGTCCGCCCTGAAGCCTCCAAGAAGCTCAATGACAT
GATGCAGTACATTAACGACTGCGGCACATCCACATCGTACACCTCGTACATTGGGAACC
TCGTGCCCACGCGCTCTCGTCGCAGTGGGGCTTACGGGCCCCTCCTTTACGATCACC
GAGGGCAACAACTCCGTCTACCGCTGCGCCGAGCTCGGCAAGTACCTCCTCGAGACCGG
CGAGGTGATGGCGTCTCGTTGCGGGTGTGATCTCTGCGGCAGTGCCGAAAACCTTT
ACGTCAAGTCTCGCCGCTTCAAGGTGTCCACCTCCGATACCCCGCGCGCCAGCTTTGAC
GCCGCCGCCGATGGCTACTTTGTGCGCGAGGGCTGCGGTGCCTTTGTGCTCAAGCGTGA
GACTAGCTGCACCAAGGACGACCGTATCTACGCTTGCATGGATGCCATCGTCCCTGGCA
ACGTCCCTAGCGCCTGCTTGC CGGAGGCCCTCGACCAGGCGCGCGTCAAGCCGGGCGAT
ATCGAGATGCTCGAGCTCAGCGCCGACTCCGCCCGCCACCTCAAGGACCCGTCCGTCT
GCCCAAGGAGCTCACTGCCGAGGAGGAAATCGGCGGCCTTCAGACGATCCTTCGTGACG
ATGACAAGCTCCCGCGCAACGTGCAACGGGCAGTGTCAAGGCCACCGTCGGTGACACC
GGTTATGCCTCTGGTGCTGCCAGCCTCATCAAGGTGCGCTTTGCATCTACAACCGCTA
CCTG'ECAGCAACGGCGACGACTGGGATGAACCCGCCCTGAGGCGCCCTGGGACAGCA
CCCTCTTTGCGTGCCAGACCTCGCGCGCTTGGCTCAAGAACCCTGGCGAGCGTCGCTAT
GCGGCCGTCTCGGGCGTCTCCGAGACGCGCTCGTGCTATTCCGTGCTCCTCTCCGAAGC
CGAGGGCCACTACGAGCGCGAGAACCGCATCTCGCTCGACGAGGAGGCGCCCAAGCTCA
TTGTGCTTCGCGCCGACTCCCACGAGGAGATCCTTGGTTCGCTCGACAAGATCCGCGAG
CGCTTCTTGACGCCACGGGCGCCGCCCGCGAGTCCGAGCTCAAGGCGCAGGCCCG
CCGCATCTTCTCGAGCTCCTCGGCGAGACCCTTGCCCAGGATGCCGCTTCTTCAGGCT
CGCAAAAGCCCTCGCTCTCAGCCTCGTCTCCACGCCCTCCAAGCTCCAGCGCGAGGTC
GAGCTCGCGGCCAAGGGTATCCCGCGCTGCCTCAAGATGCGCCGCGATTGGAGCTCCCC
TGCTGGCAGCCGCTACGCGCCTGAGCCGCTCGCCAGCGACCGCGTCGCTTCATGTACG
GCCAAGGTTCGAGCCCTTACTACGGCATCACCCAAGACATTACCGCATTTGGCCCCGAA
CTCCACGAGGTCATCAACGAAAAGACGAACCGTCTCTGGGCCGAAGGCGACCGCTGGGT
CATGCCGCGCGCCAGCTTCAAGTCGGAGCTCGAGAGCCAGCAGCAAGAGTTTGATCGCA
ACATGATTGAAATGTTCCGTCTTGGATCCTCACCTCAATTGCCTTCACCAATCTGGCG
CGCGACGTTCTCAACATCACGCCCAAGGCCGCCTTTGGCCTCAGTCTTGGCGAGATTC
CATGATTTTTCCTTTTCCAAGAAGAAGGTCTCATCTCCGACCAGCTCACCAAGGATC
TTCGCGAGTCCGACGTGTGGAACAAGGCTCTGGCCGTTGAATTTAATGCGCTGCGCGAG
GCCTGGGGCATTCCACAGAGTGTCCCCAAGGACGAGTTCTGGCAAGGCTACATTGTGCG
CGGCACCAAGCAGGATATCGAGGCGGCCATCGCCCCGGACAGCAAGTACGTGCGCCTCA
CCATCATCAATGATGCCAACACCGCCCTCATAGCGGCAAGCCCGACGCCTGCAAGGCT
GCGATCGCGCGTCTCGGTGGCAACATTCTGCGCTTCCCGTGACCCAGGGCATGTGCGG
CCACTGCCCCGAGGTGGGACCTTATACCAAGGATATCGCCAAGATCCATGCCAACCTTG

Figure 27 B-1

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AGTTCCCCGTTGTGACGGCCTTGACCTCTGGACCACAATCAACCAGAAGCGCCTCGTG
CCACGCGCCACGGGCGCCAAGGACGAATGGGCCCTTCTTCCTTTGGCGAGTACGCCGG
CCAGCTCTACGAGAAGCAGGCTAACTTCCCCCAAATCGTCGAGACCATTATACAAGCAAA
ACTACGACGTCTTTGTGAGGTTGGGCCCAACAACCACCGTAGCACCAGCAGTGCGCACC
ACGCTTGGTCCCCAGCGCAACCACCTTGCTGGCGCCATCGACAAGCAGAACGAGGATGC
TTGGACGACCATCGTCAAGCTTGTGGCTTCGCTCAAGGCCACCTTGTTCCCTGGCGTCA
CGATCTCGCCGCTGTACCACTCCAAGCTTGTGGCGGAGGCTCAGGCTTGCTACGCTGCG
CTCTGCAAGGGTGAAAAGCCCCAAGAAGAACAAGTTTGTGCGCAAGATTAGCTCAACGG
TCGCTTCAACAGCAAGGCGGACCCCATCTCCTCGGCCGATCTTGCCAGCTTTCCGCCTG
CGGACCCTGCCATTGAAGCCGCCATCTCGAGCCGCATCATGAAGCCTGTCGCTCCCAAG
TTCTACGCGCGTCTCAACATTGACGAGCAGGACGAGACCCGAGATCCGATCCTCAACAA
GGACAACGCGCCGTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTC
CGTCGCCTGCTCCTTCGGCCCCCGTGCAAAAGAAGGCTGCTCCCGCCGCGGAGACCAAG
GCTGTTGCTTCGGCTGACGCACTTCGCAAGTGCCCTGCTCGATCTCGACAGTATGCTTGC
GCTGAGCTCTGCCAGTGCCTCCGGCAACCTTGTTGAGACTGCGCCTAGCGACGCCTCGG
TCATTGTGCGCCCTGCAACATTGCGGATCTCGGCAGCCGCGCCTTCATGAAAACGTAC
GGTGTTCGGCGCCTCTGTACACGGGCGCCATGGCCAAGGGCATTGCCTCTGCGGACCT
CGTCATTGCGCGCCGCGCCAGGGCATCCTTGCGTCTTTGGCGCCGGCGGACTTCCCA
TGCAGGTTGTGCGTGAGTCCATCGAAAAGATTAGGCCGCCCTGCCCAATGGCCCCTAC
GCTGTCAACCTTATCCATTCTCCCTTTGACAGCAACCTCGAAAAGGGCAATGTGATCT
CTTCCTCGAGAAGGGTGTACCTTTGTGAGGCTCGGCCCTTATGACGCTCACCCCGC
AGGTGCTGCGGTACCGCGCGGCTGGCCTCACGCGCAACGCCGACGGCTCGGTCAACATC
CGCAACCGTATCATTGGCAAGGTCTCGCGCACCGAGCTCGCCGAGATGTTATGCGTCC
TGCGGCCGAGCACCTTCTTCAAGAGCTCATTGCTTCCGGCGAGATCAACCAGGAGCAGG
CCGAGCTCGCCCGCCGTGTTCCCGTCGCTGACGACATCGCGGTGCAAGCTGACTCGGGT
GGCCACACCGACAACCGCCCCATCCACGTCACTTGCCCCCTCATCATCAACCTTCGCGA
CCGCCTTACCGCGAGTGCGGCTACCCGGCCAACCTTCGCGTCCGTGTGGGCGCCGGCG
GTGGCATTGGGTGCCCCCAGGCGGCGCTGGCCACCTTCAACATGGGTGCCTCCTTTATT
GTCACCGGCACCGTGAACCAGGTGCGCAAGCAGTGGGCGACGTGCGACAATGTGCGCAA
GCAGCTCGCGAAGGCCACTTACTCGGACGTATGCATGGCCCCGGCTGCCGACATGTTG
AGGAAGGCGTCAAGCTTCAAGTCTCAAGAAGGGAACCATGTTTCCCTCGCGCGCCAAC
AAGCTCTACGAGCTCTTTTGCAAGTACGACTCGTTGAGTCCATGCCCCCGCAGAGCT
TGCGCGCGTCTGAGAAGCGCATCTTCAGCCGCGCGCTCGAAGAGGTCTGGGACGAGACCA
AAAACCTTTTACATTAACCGTCTTCACAACCCGAGAAGATCCAGCGCGCCGAGCGCGAC
CCCAAGCTCAAGATGTGCTGTGCTTTCGCTGGTACCTGAGCCTGGCGAGCCGCTGGGC
CAACACTGGAGCTTCCGATCGCGTCATGGACTACCAGGTCTGGTGCGGTCTTGCCATTG
GTTCTTCAACGATTTTATCAAGGGAACCTTACCTTGATCCGGCCGTGCAACGAGTAC
CCGTGCGTCTTCAAGATTAACAAGCAGATCCTTCGTGGAGCGTGCTTCTTGCGCCGTCT
CGAAATTCTGCGCAACGCACGCCTTCCGATGGCGCTGCCGCTCTTGTTGGCCAGCATCG
ATGACACATACGTCCCGGCCGAGAAGCTGTAAGTAAGCTCTCATATATGTTAGTTGCGT
GAGACCGACACGAAGATAATATCACATACGCTTTTGTGTTGTTCTTTCAATTATTTGTCT
GTGCTTCATGTTGCTCCTCAGTATCTAGCTGGCGGCTCTTATCTTCTTTAAATATCT
GGACAAGGACAAAAACAAGAATAAAGGCGAGAAGATGTGAATTTCAATTCGACTTGAGA

Figure 27 B-2

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ACTCGAAGAGCATTGATGCGGTTAGTATATGGGTATTTTCCAGACACTTTTCATCATCA
TCATCATCATCATCATTATGAAGAAGTAGTAGCTGATAAAGTAGACTCACTGTTTGCAG
CGAGAAAAAAAAAAAAAAAAAAAAA

Figure 27 B-3

[illegible]

Figure 27 C-1

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CCAGCTCAACCGCCGCACGGACCAGGGCCAGTACCTCGACGCCGTCGACATTGTCTCCG
GCAGCGGCAAGAAGAGCCTCGGCTACGCCCACGGTCCAAGACGGTCAACCCGAACGAC
TGGTTCTTCTCGTGCCACTTTTGGTTTGACTCGGTCATGCCCAGGAAGTCTCGGTGTCTGA
GTCCATGTTCCAGCTCGTCGAGGCCATCGCCGCCACGAGGATCTCGCTGGCAAAGCAC
GGCATTGCCAACCCACCTTTGTGCACGCCCCCGGCAAGATCAAGCTGGAAGTACCGC
GGSCAGCTCACGCCCAAGAGCAAGAAGATGGACTCGGAGGTCCACATCGTGTCCGTGGA
CGCCACGACGGCGTTGTGACCTCGTCGCCGACGGCTTCCTCTGGGCCGACAGCCTCC
GCGTCTACTCGGTGAGCAACATTGCGGTGCGCATCGCCTCCGGTGAGGCCCTGCCGCC
GCCTCCTCCGCCGCTCTGTGGGCTCCTCGGCTTCGTCCGTGAGCGCACGCGCTCGAG
CCCCGCTGTGCGCTCCGGCCCCGGCCAGACCATCGACCTCAAGCAGCTCAAGACCGAGC
TCCTCGAGCTCGATGCCCGCTCTACCTCTCGCAGGACCCGACCAGCGGCCAGCTCAAG
AAGCACACCGACGTGGCCTCCGGCCAGGCCACCATCGTGACGCCCTGCACGCTCGGCGA
CCTCGGTGACCGCTCCTTCATGGAGACCTACGGCGTCGTGCCCCGCTGTACACGGGCG
CCATGGCCAAGGGCATTGCCTCGGCGGACCTCGTCATCGCCGCCGGCAAGCGCAAGATC
CTCGGCTCCTTTGGCGCCGGCGGCCTCCCCATGCACCACGTGCGCGCCGCCCTCGAGAA
GATCCAGGCCGCGCTGCCTCAGGGCCCCCTACGCCGTCAACCTCATCCACTCGCCTTTTG
ACAGCAACCTCGAGAAGGGCAACGTGATCTCTTCCTCGAGAAGGGCGTCACTGTGGTG
GAGGCCTCGGCATTATGACCCTACCCCGCAGGTGTCGCGCTACCGCGCCGCCGCGCT
CTCGCGCAACGCCGACGGTTGCGTCAACATCCGCAACCGCATCATCGGCAAGGTCTCGC
GCACCGAGCTCGCCGAGATGTTTCATCCGCCCGGCCCGGAGCACCTCCTCGAGAAGCTC
ATCGCCTCGGGCGAGATCACCCAGGAGCAGGCCGAGCTCGCGCGCCGCGTTCCCGTCGC
CGACGATATCGCTGTGAGGCTGACTCGGGCGGCCACACCGACAACCGCCCCATCCACG
TCATCCTCCCGCTCATCATCAACCTCCGCAACCGCCTGCACCGCGAGTGCGGCTACCCC
GCGCACCTCCGCGTCCGCGTTGGCGCCGGCGGTGGCGTCCGCTGCCCGCAGGCCGCCG
CGCCGCGCTCACCATGGGCGCCGCTTCATCGTCAACCGGCACTGTCAACCAGGTGCGCA
AGCAGTCCGGCACCTGCGACAACGTGCGCAAGCAGCTCTCGCAGGCCACCTACTCGGAT
ATCTGCATGGCCCCGGCCGCCGACATGTTGAGGAGGGCGTCAAGCTCCAGGTCTCAA
GAAGGGAACCATGTTCCCTCGCGGCCCAACAAGCTCTACGAGCTCTTTTGCAAGTACG
ACTCCTTCGACTCCATGCCTCCTGCGGAGCTCGAGCGCATCGAGAAGCGTATCTTCAAG
CGCGCACTCCAGGAGGTCTGGGAGGAGACCAAGGACTTTTACATTAACGGTCTCAAGAA
CCCGGAGAAGATCCAGCGCGCCGAGCACGACCCCAAGCTCAAGATGTCGCTCTGCTTCC
GCTGGTACCTTGGTCTTGCCAGCCGCTGGGCCAACATGGGCGCCCCGGACCGCGTCATG
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Figure 27 C-2

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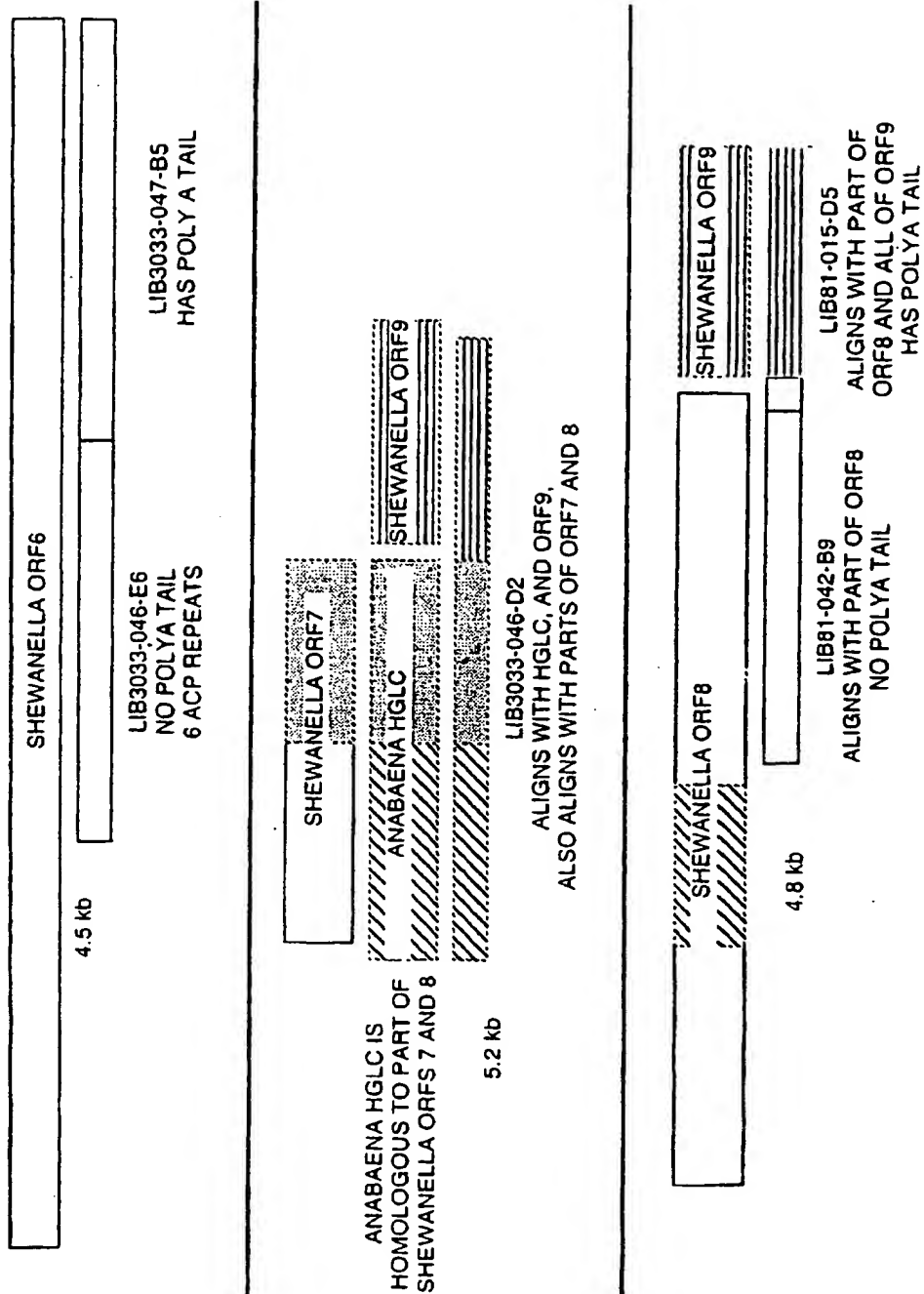


Figure 28

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Figure 29 A

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Figure 29 B

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Figure 29 C

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Facciotti, Daniel

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 cccaaatcat atctaacttt aactgcatc taattccaaa cagtatccag ccaaagcct 35460
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<210> 2

<211> 654

<212> PRT

<213> *Shewanella putrefaciens*

<400> 2

Met Lys Gln Thr Leu Met Ala Ile Ser Ile Met Ser Leu Phe Ser Phe

1

5

10

15

Asn Ala Leu Ala Ala Gln His Glu His Asp His Ile Thr Val Asp Tyr

20	25	30
Glu Gly Lys Ala Ala Thr Glu His Thr Ile Ala His Asn Gln Ala Val		
35	40	45
Ala Lys Thr Leu Asn Phe Ala Asp Thr Arg Ala Phe Glu Gln Ser Ser		
50	55	60
Lys Asn Leu Val Ala Lys Phe Asp Lys Ala Thr Ala Asp Ile Leu Arg		
65	70	75
Ala Glu Phe Ala Phe Ile Ser Asp Glu Ile Pro Asp Ser Val Asn Pro		
85	90	95
Ser Leu Tyr Arg Gln Ala Gln Leu Asn Met Val Pro Asn Gly Tyr Lys		
100	105	110
Val Ser Asp Gly Ile Tyr Gln Val Arg Gly Thr Asp Leu Ser Asn Leu		
115	120	125
Thr Leu Ile Arg Ser Asp Asn Gly Trp Ile Ala Tyr Asp Val Leu Leu		
130	135	140
Thr Lys Glu Ala Ala Lys Ala Ser Leu Gln Phe Ala Leu Lys Asn Leu		
145	150	155
Pro Lys Asp Gly Asp Pro Val Val Ala Met Ile Tyr Ser His Ser His		
165	170	175
Ala Asp His Phe Gly Gly Ala Arg Gly Val Gln Glu Met Phe Pro Asp		
180	185	190
Val Lys Val Tyr Gly Ser Asp Asn Ile Thr Lys Glu Ile Val Asp Glu		
195	200	205
Asn Val Leu Ala Gly Asn Ala Met Ser Arg Arg Ala Ala Tyr Gln Tyr		
210	215	220
Gly Ala Thr Leu Gly Lys His Asp His Gly Ile Val Asp Ala Ala Leu		
225	230	235
Gly Lys Gly Leu Ser Lys Gly Glu Ile Thr Tyr Val Ala Pro Asp Tyr		
245	250	255
Thr Leu Asn Ser Glu Gly Lys Trp Glu Thr Leu Thr Ile Asp Gly Leu		
260	265	270
Glu Met Val Phe Met Asp Ala Ser Gly Thr Glu Ala Glu Ser Glu Met		

16

530	535	540
Thr Leu Phe Asp Phe Leu Ala Val Lys Ile Asp Ser Gln Gln Ala Ala		
545	550	555 560
Lys His Gly Leu Val Lys Met Asn Val Ile Thr Pro Asp Thr Lys Asp		
565	570	575
Ile Leu Tyr Ile Glu Leu Ser Asn Gly Asn Leu Ser Asn Ala Val Val		
580	585	590
Asp Lys Glu Gln Leu Met Val Asn Lys Ala Asp Val Asn Arg Ile Leu		
595	600	605
Leu Gly Gln Val Thr Leu Lys Ala Leu Leu Ala Ser Gly Asp Ala Lys		
610	615	620
Leu Thr Gly Asp Lys Thr Ala Phe Ser Lys Ile Ala Asp Ser Met Val		
625	630	635 640
Glu Phe Thr Pro Asp Phe Glu Ile Val Pro Thr Pro Val Lys		
645	650	

<210> 3
 <211> 277
 <212> PRT
 <213> *Shewanella putrefaciens*

<400> 3
Ser Thr Lys Ala Ser Ala Arg Val Val Ala Lys Phe Asn Val Glu Glu
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Ala Ala Ile Ser Ile Gln Gln Cys Gln Gly Ile Ser Leu Ala Phe Arg
20 25 30
Tyr Ser Asp Asp Leu His Gly Leu Leu Cys His Trp Asn Asp Ala Ala
35 40 45
Asn Met Gln Gln Glu Lys Ala Glu Ile Leu Gly Leu Gly Ser Lys Gln
50 55 60
Pro Glu Ala Asn Pro Lys Asn Ser Ser Ser Glu Leu Leu Ala Leu Gly
65 70 75 80
Ile Asp Gln Lys Leu Leu Val Gln Arg Gln Asn Leu Gln His Glu Val
85 90 95

Lys His Asp Ala Ile Ala Asp Ser Ile Asp Val Cys His Ser Leu Ser
 100 105 110
 Lys Pro Ala Asn Val Gly Leu Phe Thr Glu Ser Leu Ala Ser Phe Asp
 115 120 125
 Phe Ala Phe Ser Lys Leu Ser Leu Ala Leu Gly Leu Gly Lys Ala Lys
 130 135 140
 Ile Tyr Ser Glu Lys Leu Ala Trp Leu Asp Phe Phe Arg Asp Arg Gln
 145 150 155 160
 Leu Ala Glu Pro Leu Ala Leu Leu Ala Arg Lys Glu Ser Glu Ser Phe
 165 170 175
 Tyr His Ser Leu Ile Ser His Ile Asn Thr Ser Asn Arg Cys Arg Glu
 180 185 190
 Ile Asp Val Gly Phe Glu Ile Ser Ala Ser Asp Thr Glu Glu Lys Ser
 195 200 205
 Ala Gln Ser Ala Gly Lys Asn Asp Ala Thr Cys Ile Gly Val Leu Leu
 210 215 220
 Trp Asp Gly Ser His Ser Val Asn Phe His Val Gly Thr Gln Ala Phe
 225 230 235 240
 Gln Ala Asp Ser Leu Arg Pro Lys Gly Lys Asp Gly Tyr Glu Phe Arg
 245 250 255
 Trp Glu Asn Pro Arg Ile Glu Ser His Gln Ser Leu Leu Ala Arg Leu
 260 265 270
 Tyr Gly Arg Val Met
 275

<210> 4

<211> 1480

<212> DNA

<213> *Shewanella putrefaciens*

<400> 4

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 agatgggaaar gvavaaaysh asnvaggaaa asrgngncys gngysraaha rgtyrsrasa 180
 shscccagta aacaatgccca attatcagca gcgttcattt gctgttcttt agcctcaatc 240
 aaacctaatac cagacttttg tggctcagcg ttaggcttat taggycyshs trasnasaaa 300

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aasnmtgngn gysaaggygy srysgnrgaa asnrysasns raactcgact ctagtaaagc 360
aagaccaata tcttgtttta acaaaacctg tcgctgatta agttgatgct caaccttggtg 420
atccgcaata gcatcggaata tsrsrgaagy asgnysvagn arggnasngn hsgvayshsa 480
saaaaassra tcaacacaat ggctcaagct tttaggtgca ttaactccaa gaaaagtttc 540
gctcagtgcg gagaagtcaa acgcaaaaga ttttagcgat aatgccagca svacyshssr 600
srysraasn vagyhthrgs raasrhasha ahsryssraa ccaagtcctt tcgctttaat 660
gtaagactcc ttgagcgccc acaaatcaaa aaagcggctc cgctgcaagg cctctggtaa 720
cgctaacaag gctcgctttt gygyysaays tyrsrgysaa trashharga sarggnaagr 780
aaaaargysg ctgattcaga gaaataatga ctaagaatag agtggatatt ggtgctgtta 840
cggcaacgct caatgtcgac gccaaactca atactagcag agtcagtttc srgsrhtyrh 900
ssrsrhasn thrsrasnar gcysarggas vagyhgsraa srasthrct ccttgcttgc 960
ctgactggcg cctttattat cagcagtgcg aatgcctact aatagccaat ctccactatg 1020
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vatrasgyr hssrvaasnh hsvagythrg ngcaaattgc gcatcactca atctaggctt 1140
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gygnthrysa aggnystyra rgasnvaysg asgrtrsrys vagtgtagtc tgggtatcgc 1440
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<210> 5

<211> 970

<212> PRT

<213> *Shewanella putrefaciens*

<400> 5

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Met Ser Met Phe Leu Asn Ser Lys Leu Ser Arg Ser Val Lys Leu Ala
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Ile Ser Ala Gly Leu Thr Ala Ser Leu Ala Met Pro Val Phe Ala Glu
          20             25             30

```

```

Glu Thr Ala Ala Glu Glu Gln Ile Glu Arg Val Ala Val Thr Gly Ser
          35             40             45

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Arg Ile Ala Lys Ala Glu Leu Thr Gln Pro Ala Pro Val Val Ser Leu
          50             55             60

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```

Ser Ala Glu Glu Leu Thr Lys Phe Gly Asn Gln Asp Leu Gly Ser Val
          65             70             75             80

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```

Leu Ala Glu Leu Pro Ala Ile Gly Ala Thr Asn Thr Ile Ile Gly Asn
          85             90             95

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Asn Asn Ser Asn Ser Ser Ala Gly Val Ser Ser Ala Asp Leu Arg Arg
          100            105            110

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Leu Gly Ala Asn Arg Thr Leu Val Leu Val Asn Gly Lys Arg Tyr Val
 115 120 125

Ala Gly Gln Pro Gly Ser Ala Glu Val Asp Leu Ser Thr Ile Pro Thr
 130 135 140

Ser Met Ile Ser Arg Val Glu Ile Val Thr Gly Gly Ala Ser Ala Ile
 145 150 155 160

Tyr Gly Ser Asp Ala Val Ser Gly Val Ile Asn Val Ile Leu Lys Glu
 165 170 175

Asp Phe Glu Gly Phe Glu Phe Asn Ala Arg Thr Ser Gly Ser Thr Glu
 180 185 190

Ser Val Gly Thr Gln Glu His Ser Phe Asp Ile Leu Gly Gly Ala Asn
 195 200 205

Val Ala Asp Gly Arg Gly Asn Val Thr Phe Tyr Ala Gly Tyr Glu Arg
 210 215 220

Thr Lys Glu Val Met Ala Thr Asp Ile Arg Gln Phe Asp Ala Trp Gly
 225 230 235 240

Thr Ile Lys Asn Glu Ala Asp Gly Gly Glu Asp Asp Gly Ile Pro Asp
 245 250 255

Arg Leu Arg Val Pro Arg Val Tyr Ser Glu Met Ile Asn Ala Thr Gly
 260 265 270

Val Ile Asn Ala Phe Gly Gly Gly Ile Gly Arg Ser Thr Phe Asp Ser
 275 280 285

Asn Gly Asn Pro Ile Ala Gln Gln Glu Arg Asp Gly Thr Asn Ser Phe
 290 295 300

Ala Phe Gly Ser Phe Pro Asn Gly Cys Asp Thr Cys Phe Asn Thr Glu
 305 310 315 320

Ala Tyr Glu Asn Tyr Ile Pro Gly Val Glu Arg Ile Asn Val Gly Ser
 325 330 335

Ser Phe Asn Phe Asp Phe Thr Asp Asn Ile Gln Phe Tyr Thr Asp Phe
 340 345 350

Arg Tyr Val Lys Ser Asp Ile Gln Gln Gln Phe Gln Pro Ser Phe Arg
 355 360 365

Phe Gly Asn Ile Asn Ile Asn Val Glu Asp Asn Ala Phe Leu Asn Asp
 370 375 380

Asp Leu Arg Gln Gln Met Leu Asp Ala Gly Gln Thr Asn Ala Ser Phe
 385 390 395 400

Ala Lys Phe Phe Asp Glu Leu Gly Asn Arg Ser Ala Glu Asn Lys Arg
 405 410 415

Glu Leu Phe Arg Tyr Val Gly Gly Phe Lys Gly Gly Phe Asp Ile Ser
 420 425 430

Glu Thr Ile Phe Asp Tyr Asp Leu Tyr Tyr Val Tyr Gly Glu Thr Asn
 435 440 445

Asn Arg Arg Lys Thr Leu Asn Asp Leu Ile Pro Asp Asn Phe Val Ala
 450 455 460

Ala Val Asp Ser Val Ile Asp Pro Asp Thr Gly Leu Ala Ala Cys Arg
 465 470 475 480

Ser Gln Val Ala Ser Ala Gln Gly Asp Asp Tyr Thr Asp Pro Ala Ser
 485 490 495

Val Asn Gly Ser Asp Cys Val Ala Tyr Asn Pro Phe Gly Met Gly Gln
 500 505 510

Ala Ser Ala Glu Ala Arg Asp Trp Val Ser Ala Asp Val Thr Arg Glu
 515 520 525

Asp Lys Ile Thr Gln Gln Val Ile Gly Gly Thr Leu Gly Thr Asp Ser
 530 535 540

Glu Glu Leu Phe Glu Leu Gln Gly Gly Ala Ile Ala Met Val Val Gly
 545 550 555 560

Phe Glu Tyr Arg Glu Glu Thr Ser Gly Ser Thr Thr Asp Glu Phe Thr
 565 570 575

Lys Ala Gly Phe Leu Thr Ser Ala Ala Thr Pro Asp Ser Tyr Gly Glu
 580 585 590

Tyr Asp Val Thr Glu Tyr Phe Val Glu Val Asn Ile Pro Val Leu Lys
 595 600 605

Glu Leu Pro Phe Ala His Glu Leu Ser Phe Asp Gly Ala Tyr Arg Asn
 610 615 620

Ala Asp Tyr Ser His Ala Gly Lys Thr Glu Ala Trp Lys Ala Gly Met
 625 630 635 640

Phe Tyr Ser Pro Leu Glu Gln Leu Ala Leu Arg Gly Thr Val Gly Glu
 645 650 655

Ala Val Arg Ala Pro Asn Ile Ala Glu Ala Phe Ser Pro Arg Ser Pro
 660 665 670

Gly Phe Gly Arg Val Ser Asp Pro Cys Asp Ala Asp Asn Ile Asn Asp
 675 680 685

Asp Pro Asp Arg Val Ser Asn Cys Ala Ala Leu Gly Ile Pro Pro Gly
 690 695 700

Phe Gln Ala Asn Asp Asn Val Ser Val Asp Thr Leu Ser Gly Gly Asn
 705 710 715 720

Pro Asp Leu Lys Pro Glu Thr Ser Thr Ser Phe Thr Gly Gly Leu Val
 725 730 735

Trp Thr Pro Thr Phe Ala Asp Asn Leu Ser Phe Thr Val Asp Tyr Tyr
 740 745 750

Asp Ile Gln Ile Glu Asp Ala Ile Leu Ser Val Ala Thr Gln Thr Val
 755 760 765

Ala Asp Asn Cys Val Asp Ser Thr Gly Gly Pro Asp Thr Asp Phe Cys
 770 775 780

Ser Gln Val Asp Arg Asn Pro Thr Thr Tyr Asp Ile Glu Leu Val Arg
 785 790 795 800

Ser Gly Tyr Leu Asn Ala Ala Ala Leu Asn Thr Lys Gly Ile Glu Phe
 805 810 815

Gln Ala Ala Tyr Ser Leu Asp Leu Glu Ser Phe Asn Ala Pro Gly Glu
 820 825 830

Leu Arg Phe Asn Leu Leu Gly Asn Gln Leu Leu Glu Leu Glu Arg Leu
 835 840 845

Glu Phe Gln Asn Arg Pro Asp Glu Ile Asn Asp Glu Lys Gly Glu Val
 850 855 860

Gly Asp Pro Glu Leu Gln Phe Arg Leu Gly Ile Asp Tyr Arg Leu Asp
 865 870 875 880

Lys Arg Tyr Gly Val Ser Arg Val Ser Asp Ile Gln Ser Pro His Val
 130 135 140

Pro Met Arg Tyr Phe Asn Gln Ile Pro Val Thr Gln Gly Ser Asp Val
 145 150 155 160

Gln Thr Tyr Thr Leu His Tyr Glu Thr Leu Ala Lys Thr Leu Ala Leu
 165 170 175

Pro Ser Thr Asp Gly Asp Asn Val Val Gln Val Val Ser Leu Thr Ile
 180 185 190

Pro Pro Lys Leu Thr Glu Glu Ala Pro Ser Ser Ile Leu Leu Gly Ile
 195 200 205

Asp Pro His Ser Asp Trp Ile Tyr Leu Asp Ile Tyr Gln Asp Gly Asn
 210 215 220

Thr Gln Ala Thr Asn Arg Tyr Met Ala Tyr Val Leu Lys His Gly Pro
 225 230 235 240

Phe His Leu Arg Lys Leu Leu Val Arg Asn Tyr His Thr Phe Leu Gln
 245 250 255

Arg Phe Pro Gly Ala Thr Gln Asn Arg Arg Pro Ser Lys Asp Met Pro
 260 265 270

Glu Thr Ile Asn Lys Thr Pro Glu Thr Gln Ala Pro Ser Gly Asp Ser
 275 280 285

<210> 7

<211> 2756

<212> PRT

<213> *Shewanella putrefaciens*

<400> 7

Met Ser Gln Thr Ser Lys Pro Thr Asn Ser Ala Thr Glu Gln Ala Gln
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Asp Ser Gln Ala Asp Ser Arg Leu Asn Lys Arg Leu Lys Asp Met Pro
 20 25 30

Ile Ala Ile Val Gly Met Ala Ser Ile Phe Ala Asn Ser Arg Tyr Leu

	35		40		45														
Asn	Lys	Phe	Trp	Asp	Leu	Ile	Ser	Glu	Lys	Ile	Asp	Ala	Ile	Thr	Glu				
50						55					60								
Leu	Pro	Ser	Thr	His	Trp	Gln	Pro	Glu	Glu	Tyr	Tyr	Asp	Ala	Asp	Lys				
65					70					75					80				
Thr	Ala	Ala	Asp	Lys	Ser	Tyr	Cys	Lys	Arg	Gly	Gly	Phe	Leu	Pro	Asp				
				85					90					95					
Val	Asp	Phe	Asn	Pro	Met	Glu	Phe	Gly	Leu	Pro	Pro	Asn	Ile	Leu	Glu				
			100					105					110						
Leu	Thr	Asp	Ser	Ser	Gln	Leu	Leu	Ser	Leu	Ile	Val	Ala	Lys	Glu	Val				
		115				120					125								
Leu	Ala	Asp	Ala	Asn	Leu	Pro	Glu	Asn	Tyr	Asp	Arg	Asp	Lys	Ile	Gly				
	130				135						140								
Ile	Thr	Leu	Gly	Val	Gly	Gly	Gly	Gln	Lys	Ile	Ser	His	Ser	Leu	Thr				
145					150					155				160					
Ala	Arg	Leu	Gln	Tyr	Pro	Val	Leu	Lys	Lys	Val	Phe	Ala	Asn	Ser	Gly				
			165						170					175					
Ile	Ser	Asp	Thr	Asp	Ser	Glu	Met	Leu	Ile	Lys	Lys	Phe	Gln	Asp	Gln				
		180						185					190						
Tyr	Val	His	Trp	Glu	Glu	Asn	Ser	Phe	Pro	Gly	Ser	Leu	Gly	Asn	Val				
		195					200					205							
Ile	Ala	Gly	Arg	Ile	Ala	Asn	Arg	Phe	Asp	Phe	Gly	Gly	Met	Asn	Cys				
	210					215					220								
Val	Val	Asp	Ala	Ala	Cys	Ala	Gly	Ser	Leu	Ala	Ala	Met	Arg	Met	Ala				
225					230					235				240					
Leu	Thr	Glu	Leu	Thr	Glu	Gly	Arg	Ser	Glu	Met	Met	Ile	Thr	Gly	Gly				
			245						250					255					
Val	Cys	Thr	Asp	Asn	Ser	Pro	Ser	Met	Tyr	Met	Ser	Phe	Ser	Lys	Thr				
		260						265					270						
Pro	Ala	Phe	Thr	Thr	Asn	Glu	Thr	Ile	Gln	Pro	Phe	Asp	Ile	Asp	Ser				
	275					280						285							
Lys	Gly	Met	Met	Ile	Gly	Glu	Gly	Ile	Gly	Met	Val	Ala	Leu	Lys	Arg				

290	295	300
Leu Glu Asp Ala Glu Arg Asp Gly Asp Arg Ile Tyr Ser Val Ile Lys		
305	310	315 320
Gly Val Gly Ala Ser Ser Asp Gly Lys Phe Lys Ser Ile Tyr Ala Pro		
	325	330 335
Arg Pro Ser Gly Gln Ala Lys Ala Leu Asn Arg Ala Tyr Asp Asp Ala		
	340	345 350
Gly Phe Ala Pro His Thr Leu Gly Leu Ile Glu Ala His Gly Thr Gly		
	355	360 365
Thr Ala Ala Gly Asp Ala Ala Glu Phe Ala Gly Leu Cys Ser Val Phe		
	370	375 380
Ala Glu Gly Asn Asp Thr Lys Gln His Ile Ala Leu Gly Ser Val Lys		
	385	390 395 400
Ser Gln Ile Gly His Thr Lys Ser Thr Ala Gly Thr Ala Gly Leu Ile		
	405	410 415
Lys Ala Ala Leu Ala Leu His His Lys Val Leu Pro Pro Thr Ile Asn		
	420	425 430
Val Ser Gln Pro Ser Pro Lys Leu Asp Ile Glu Asn Ser Pro Phe Tyr		
	435	440 445
Leu Asn Thr Glu Thr Arg Pro Trp Leu Pro Arg Val Asp Gly Thr Pro		
	450	455 460
Arg Arg Ala Gly Ile Ser Ser Phe Gly Phe Gly Gly Thr Asn Phe His		
	465	470 475 480
Phe Val Leu Glu Glu Tyr Asn Gln Glu His Ser Arg Thr Asp Ser Glu		
	485	490 495
Lys Ala Lys Tyr Arg Gln Arg Gln Val Ala Gln Ser Phe Leu Val Ser		
	500	505 510
Ala Ser Asp Lys Ala Ser Leu Ile Asn Glu Leu Asn Val Leu Ala Ala		
	515	520 525
Ser Ala Ser Gln Ala Glu Phe Ile Leu Lys Asp Ala Ala Ala Asn Tyr		
	530	535 540
Gly Val Arg Glu Leu Asp Lys Asn Ala Pro Arg Ile Gly Leu Val Ala		

545	550	555	560
Asn Thr Ala Glu Glu Leu Ala Gly Leu Ile Lys Gln Ala Leu Ala Lys			
565	570	575	
Leu Ala Ala Ser Asp Asp Asn Ala Trp Gln Leu Pro Gly Gly Thr Ser			
580	585	590	
Tyr Arg Ala Ala Ala Val Glu Gly Lys Val Ala Ala Leu Phe Ala Gly			
595	600	605	
Gln Gly Ser Gln Tyr Leu Asn Met Gly Arg Asp Leu Thr Cys Tyr Tyr			
610	615	620	
Pro Glu Met Arg Gln Gln Phe Val Thr Ala Asp Lys Val Phe Ala Ala			
625	630	635	640
Asn Asp Lys Thr Pro Leu Ser Gln Thr Leu Tyr Pro Lys Pro Val Phe			
645	650	655	
Asn Lys Asp Glu Leu Lys Ala Gln Glu Ala Ile Leu Thr Asn Thr Ala			
660	665	670	
Asn Ala Gln Ser Ala Ile Gly Ala Ile Ser Met Gly Gln Tyr Asp Leu			
675	680	685	
Phe Thr Ala Ala Gly Phe Asn Ala Asp Met Val Ala Gly His Ser Phe			
690	695	700	
Gly Glu Leu Ser Ala Leu Cys Ala Ala Gly Val Ile Ser Ala Asp Asp			
705	710	715	720
Tyr Tyr Lys Leu Ala Phe Ala Arg Gly Glu Ala Met Ala Thr Lys Ala			
725	730	735	
Pro Ala Lys Asp Gly Val Glu Ala Asp Ala Gly Ala Met Phe Ala Ile			
740	745	750	
Ile Thr Lys Ser Ala Ala Asp Leu Glu Thr Val Glu Ala Thr Ile Ala			
755	760	765	
Lys Phe Asp Gly Val Lys Val Ala Asn Tyr Asn Ala Pro Thr Gln Ser			
770	775	780	
Val Ile Ala Gly Pro Thr Ala Thr Thr Ala Asp Ala Ala Lys Ala Leu			
785	790	795	800
Thr Glu Leu Gly Tyr Lys Ala Ile Asn Leu Pro Val Ser Gly Ala Phe			

805	810	815
His Thr Glu Leu Val Gly His Ala Gln Ala Pro Phe Ala Lys Ala Ile 820	825	830
Asp Ala Ala Lys Phe Thr Lys Thr Ser Arg Ala Leu Tyr Ser Asn Ala 835	840	845
Thr Gly Gly Leu Tyr Glu Ser Thr Ala Ala Lys Ile Lys Ala Ser Phe 850	855	860
Lys Lys His Met Leu Gln Ser Val Arg Phe Thr Ser Gln Leu Glu Ala 865	870	875 880
Met Tyr Asn Asp Gly Ala Arg Val Phe Val Glu Phe Gly Pro Lys Asn 885	890	895
Ile Leu Gln Lys Leu Val Gln Gly Thr Leu Val Asn Thr Glu Asn Glu 900	905	910
Val Cys Thr Ile Ser Ile Asn Pro Asn Pro Lys Val Asp Ser Asp Leu 915	920	925
Gln Leu Lys Gln Ala Ala Met Gln Leu Ala Val Thr Gly Val Val Leu 930	935	940
Ser Glu Ile Asp Pro Tyr Gln Ala Asp Ile Ala Ala Pro Ala Lys Lys 945	950	955 960
Ser Pro Met Ser Ile Ser Leu Asn Ala Ala Asn His Ile Ser Lys Ala 965	970	975
Thr Arg Ala Lys Met Ala Lys Ser Leu Glu Thr Gly Ile Val Thr Ser 980	985	990
Gln Ile Glu His Val Ile Glu Glu Lys Ile Val Glu Val Glu Lys Leu 995	1000	1005
Val Glu Val Glu Lys Ile Val Glu Lys Val Val Glu Val Glu Lys Val 1010	1015	1020
Val Glu Val Glu Ala Pro Val Asn Ser Val Gln Ala Asn Ala Ile Gln 1025	1030	1035 1040
Thr Arg Ser Val Val Ala Pro Val Ile Glu Asn Gln Val Val Ser Lys 1045	1050	1055
Asn Ser Lys Pro Ala Val Gln Ser Ile Ser Gly Asp Ala Leu Ser Asn		

1060	1065	1070
Phe Phe Ala Ala Gln Gln Gln Thr Ala Gln Leu His Gln Gln Phe Leu		
1075	1080	1085
Ala Ile Pro Gln Gln Tyr Gly Glu Thr Phe Thr Thr Leu Met Thr Glu		
1090	1095	1100
Gln Ala Lys Leu Ala Ser Ser Gly Val Ala Ile Pro Glu Ser Leu Gln		
1105	1110	1115
Arg Ser Met Glu Gln Phe His Gln Leu Gln Ala Gln Thr Leu Gln Ser		
1125	1130	1135
His Thr Gln Phe Leu Glu Met Gln Ala Gly Ser Asn Ile Ala Ala Leu		
1140	1145	1150
Asn Leu Leu Asn Ser Ser Gln Ala Thr Tyr Ala Pro Ala Ile His Asn		
1155	1160	1165
Glu Ala Ile Gln Ser Gln Val Val Gln Ser Gln Thr Ala Val Gln Pro		
1170	1175	1180
Val Ile Ser Thr Gln Val Asn His Val Ser Glu Gln Pro Thr Gln Ala		
1185	1190	1195
Pro Ala Pro Lys Ala Gln Pro Ala Pro Val Thr Thr Ala Val Gln Thr		
1205	1210	1215
Ala Pro Ala Gln Val Val Arg Gln Ala Ala Pro Val Gln Ala Ala Ile		
1220	1225	1230
Glu Pro Ile Asn Thr Ser Val Ala Thr Thr Thr Pro Ser Ala Phe Ser		
1235	1240	1245
Ala Glu Thr Ala Leu Ser Ala Thr Lys Val Gln Ala Thr Met Leu Glu		
1250	1255	1260
Val Val Ala Glu Lys Thr Gly Tyr Pro Thr Glu Met Leu Glu Leu Glu		
1265	1270	1275
Met Asp Met Glu Ala Asp Leu Gly Ile Asp Ser Ile Lys Arg Val Glu		
1285	1290	1295
Ile Leu Gly Thr Val Gln Asp Glu Leu Pro Gly Leu Pro Glu Leu Ser		
1300	1305	1310
Pro Glu Asp Leu Ala Glu Cys Arg Thr Leu Gly Glu Ile Val Asp Tyr		

1315	1320	1325
Met Gly Ser Lys Leu Pro Ala Glu Gly Ser Met Asn Ser Gln Leu Ser		
1330	1335	1340
Thr Gly Ser Ala Ala Ala Thr Pro Ala Ala Asn Gly Leu Ser Ala Glu		
1345	1350	1355 1360
Lys Val Gln Ala Thr Met Met Ser Val Val Ala Glu Lys Thr Gly Tyr		
1365	1370	1375
Pro Thr Glu Met Leu Glu Leu Glu Met Asp Met Glu Ala Asp Leu Gly		
1380	1385	1390
Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Gly Thr Val Gln Asp Glu		
1395	1400	1405
Leu Pro Gly Leu Pro Glu Leu Ser Pro Glu Asp Leu Ala Glu Cys Arg		
1410	1415	1420
Thr Leu Gly Glu Ile Val Asp Tyr Met Asn Ser Lys Leu Ala Asp Gly		
1425	1430	1435 1440
Ser Lys Leu Pro Ala Glu Gly Ser Met Asn Ser Gln Leu Ser Thr Ser		
1445	1450	1455
Ala Ala Ala Ala Thr Pro Ala Ala Asn Gly Leu Ser Ala Glu Lys Val		
1460	1465	1470
Gln Ala Thr Met Met Ser Val Val Ala Glu Lys Thr Gly Tyr Pro Thr		
1475	1480	1485
Glu Met Leu Glu Leu Glu Met Asp Met Glu Ala Asp Leu Gly Ile Asp		
1490	1495	1500
Ser Ile Lys Arg Val Glu Ile Leu Gly Thr Val Gln Asp Glu Leu Pro		
1505	1510	1515 1520
Gly Leu Pro Glu Leu Asn Pro Glu Asp Leu Ala Glu Cys Arg Thr Leu		
1525	1530	1535
Gly Glu Ile Val Thr Tyr Met Asn Ser Lys Leu Ala Asp Gly Ser Lys		
1540	1545	1550
Leu Pro Ala Glu Gly Ser Met His Tyr Gln Leu Ser Thr Ser Thr Ala		
1555	1560	1565
Ala Ala Thr Pro Val Ala Asn Gly Leu Ser Ala Glu Lys Val Gln Ala		

1570	1575	1580
Thr Met Met Ser Val Val Ala Asp Lys Thr Gly Tyr Pro Thr Glu Met		
1585	1590	1595 1600
Leu Glu Leu Glu Met Asp Met Glu Ala Asp Leu Gly Ile Asp Ser Ile		
1605	1610	1615
Lys Arg Val Glu Ile Leu Gly Thr Val Gln Asp Glu Leu Pro Gly Leu		
1620	1625	1630
Pro Glu Leu Asn Pro Glu Asp Leu Ala Glu Cys Arg Thr Leu Gly Glu		
1635	1640	1645
Ile Val Asp Tyr Met Gly Ser Lys Leu Pro Ala Glu Gly Ser Ala Asn		
1650	1655	1660
Thr Ser Ala Ala Ala Ser Leu Asn Val Ser Ala Val Ala Ala Pro Gln		
1665	1670	1675 1680
Ala Ala Ala Thr Pro Val Ser Asn Gly Leu Ser Ala Glu Lys Val Gln		
1685	1690	1695
Ser Thr Met Met Ser Val Val Ala Glu Lys Thr Gly Tyr Pro Thr Glu		
1700	1705	1710
Met Leu Glu Leu Gly Met Asp Met Glu Ala Asp Leu Gly Ile Asp Ser		
1715	1720	1725
Ile Lys Arg Val Glu Ile Leu Gly Thr Val Gln Asp Glu Leu Pro Gly		
1730	1735	1740
Leu Pro Glu Leu Asn Pro Glu Asp Leu Ala Glu Cys Arg Thr Leu Gly		
1745	1750	1755 1760
Glu Ile Val Asp Tyr Met Asn Ser Lys Leu Ala Asp Gly Ser Lys Leu		
1765	1770	1775
Pro Ala Glu Gly Ser Ala Asn Thr Ser Ala Thr Ala Ala Thr Pro Ala		
1780	1785	1790
Val Asn Gly Leu Ser Ala Asp Lys Val Gln Ala Thr Met Met Ser Val		
1795	1800	1805
Val Ala Glu Lys Thr Gly Tyr Pro Thr Glu Met Leu Glu Leu Gly Met		
1810	1815	1820
Asp Met Glu Ala Asp Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile		

1825	1830	1835	1840
Leu Gly Thr Val Gln Asp Glu Leu Pro Gly Leu Pro Glu Leu Asn Pro			
1845	1850	1855	
Glu Asp Leu Ala Glu Cys Arg Thr Leu Gly Glu Ile Val Ser Tyr Met			
1860	1865	1870	
Asn Ser Gln Leu Ala Asp Gly Ser Lys Leu Ser Thr Ser Ala Ala Glu			
1875	1880	1885	
Gly Ser Ala Asp Thr Ser Ala Ala Asn Ala Ala Lys Pro Ala Ala Ile			
1890	1895	1900	
Ser Ala Glu Pro Ser Val Glu Leu Pro Pro His Ser Glu Val Ala Leu			
1905	1910	1915	1920
Lys Lys Leu Asn Ala Ala Asn Lys Leu Glu Asn Cys Phe Ala Ala Asp			
1925	1930	1935	
Ala Ser Val Val Ile Asn Asp Asp Gly His Asn Ala Gly Val Leu Ala			
1940	1945	1950	
Glu Lys Leu Ile Lys Gln Gly Leu Lys Val Ala Val Val Arg Leu Pro			
1955	1960	1965	
Lys Gly Gln Pro Gln Ser Pro Leu Ser Ser Asp Val Ala Ser Phe Glu			
1970	1975	1980	
Leu Ala Ser Ser Gln Glu Ser Glu Leu Glu Ala Ser Ile Thr Ala Val			
1985	1990	1995	2000
Ile Ala Gln Ile Glu Thr Gln Val Gly Ala Ile Gly Gly Phe Ile His			
2005	2010	2015	
Leu Gln Pro Glu Ala Asn Thr Glu Glu Gln Thr Ala Val Asn Leu Asp			
2020	2025	2030	
Ala Gln Ser Phe Thr His Val Ser Asn Ala Phe Leu Trp Ala Lys Leu			
2035	2040	2045	
Leu Gln Pro Lys Leu Val Ala Gly Ala Asp Ala Arg Arg Cys Phe Val			
2050	2055	2060	
Thr Val Ser Arg Ile Asp Gly Gly Phe Gly Tyr Leu Asn Thr Asp Ala			
2065	2070	2075	2080
Leu Lys Asp Ala Glu Leu Asn Gln Ala Ala Leu Ala Gly Leu Thr Lys			

	2085	2090	2095
Thr Leu Ser His Glu Trp Pro Gln Val Phe Cys Arg Ala Leu Asp Ile	2100	2105	2110
Ala Thr Asp Val Asp Ala Thr His Leu Ala Asp Ala Ile Thr Ser Glu	2115	2120	2125
Leu Phe Asp Ser Gln Ala Gln Leu Pro Glu Val Gly Leu Ser Leu Ile	2130	2135	2140
Asp Gly Lys Val Asn Arg Val Thr Leu Val Ala Ala Glu Ala Ala Asp	2145	2150	2155 2160
Lys Thr Ala Lys Ala Glu Leu Asn Ser Thr Asp Lys Ile Leu Val Thr	2165	2170	2175
Gly Gly Ala Lys Gly Val Thr Phe Glu Cys Ala Leu Ala Leu Ala Ser	2180	2185	2190
Arg Ser Gln Ser His Phe Ile Leu Ala Gly Arg Ser Glu Leu Gln Ala	2195	2200	2205
Leu Pro Ser Trp Ala Glu Gly Lys Gln Thr Ser Glu Leu Lys Ser Ala	2210	2215	2220
Ala Ile Ala His Ile Ile Ser Thr Gly Gln Lys Pro Thr Pro Lys Gln	2225	2230	2235 2240
Val Glu Ala Ala Val Trp Pro Val Gln Ser Ser Ile Glu Ile Asn Ala	2245	2250	2255
Ala Leu Ala Ala Phe Asn Lys Val Gly Ala Ser Ala Glu Tyr Val Ser	2260	2265	2270
Met Asp Val Thr Asp Ser Ala Ala Ile Thr Ala Ala Leu Asn Gly Arg	2275	2280	2285
Ser Asn Glu Ile Thr Gly Leu Ile His Gly Ala Gly Val Leu Ala Asp	2290	2295	2300
Lys His Ile Gln Asp Lys Thr Leu Ala Glu Leu Ala Lys Val Tyr Gly	2305	2310	2315 2320
Thr Lys Val Asn Gly Leu Lys Ala Leu Leu Ala Ala Leu Glu Pro Ser	2325	2330	2335
Lys Ile Lys Leu Leu Ala Met Phe Ser Ser Ala Ala Gly Phe Tyr Gly			

2340	2345	2350
Asn Ile Gly Gln Ser Asp Tyr Ala Met Ser Asn Asp Ile Leu Asn Lys		
2355	2360	2365
Ala Ala Leu Gln Phe Thr Ala Arg Asn Pro Gln Ala Lys Val Met Ser		
2370	2375	2380
Phe Asn Trp Gly Pro Trp Asp Gly Gly Met Val Asn Pro Ala Leu Lys		
2385	2390	2395
Lys Met Phe Thr Glu Arg Gly Val Tyr Val Ile Pro Leu Lys Ala Gly		
2405	2410	2415
Ala Glu Leu Phe Ala Thr Gln Leu Leu Ala Glu Thr Gly Val Gln Leu		
2420	2425	2430
Leu Ile Gly Thr Ser Met Gln Gly Gly Ser Asp Thr Lys Ala Thr Glu		
2435	2440	2445
Thr Ala Ser Val Lys Lys Leu Asn Ala Gly Glu Val Leu Ser Ala Ser		
2450	2455	2460
His Pro Arg Ala Gly Ala Gln Lys Thr Pro Leu Gln Ala Val Thr Ala		
2465	2470	2475
Thr Arg Leu Leu Thr Pro Ser Ala Met Val Phe Ile Glu Asp His Arg		
2485	2490	2495
Ile Gly Gly Asn Ser Val Leu Pro Thr Val Cys Ala Ile Asp Trp Met		
2500	2505	2510
Arg Glu Ala Ala Ser Asp Met Leu Gly Ala Gln Val Lys Val Leu Asp		
2515	2520	2525
Tyr Lys Leu Leu Lys Gly Ile Val Phe Glu Thr Asp Glu Pro Gln Glu		
2530	2535	2540
Leu Thr Leu Glu Leu Thr Pro Asp Asp Ser Asp Glu Ala Thr Leu Gln		
2545	2550	2555
Ala Leu Ile Ser Cys Asn Gly Arg Pro Gln Tyr Lys Ala Thr Leu Ile		
2565	2570	2575
Ser Asp Asn Ala Asp Ile Lys Gln Leu Asn Lys Gln Phe Asp Leu Ser		
2580	2585	2590
Ala Lys Ala Ile Thr Thr Ala Lys Glu Leu Tyr Ser Asn Gly Thr Leu		

2595 2600 2605
 Phe His Gly Pro Arg Leu Gln Gly Ile Gln Ser Val Val Gln Phe Asp
 2610 2615 2620
 Asp Gln Gly Leu Ile Ala Lys Val Ala Leu Pro Lys Val Glu Leu Ser
 2625 2630 2635 2640
 Asp Cys Gly Glu Phe Leu Pro Gln Thr His Met Gly Gly Ser Gln Pro
 2645 2650 2655
 Phe Ala Glu Asp Leu Leu Leu Gln Ala Met Leu Val Trp Ala Arg Leu
 2660 2665 2670
 Lys Thr Gly Ser Ala Ser Leu Pro Ser Ser Ile Gly Glu Phe Thr Ser
 2675 2680 2685
 Tyr Gln Pro Met Ala Phe Gly Glu Thr Gly Thr Ile Glu Leu Glu Val
 2690 2695 2700
 Ile Lys His Asn Lys Arg Ser Leu Glu Ala Asn Val Ala Leu Tyr Arg
 2705 2710 2715 2720
 Asp Asn Gly Glu Leu Ser Ala Met Phe Lys Ser Ala Lys Ile Thr Ile
 2725 2730 2735
 Ser Lys Ser Leu Asn Ser Ala Phe Leu Pro Ala Val Leu Ala Asn Asp
 2740 2745 2750
 Ser Glu Ala Asn
 2755

<210> 8

<211> 771

<212> PRT

<213> *Shewanella putrefaciens*

<400> 8

Met Pro Leu Arg Ile Ala Leu Ile Leu Leu Pro Thr Pro Gln Phe Glu
 1 5 10 15
 Val Asn Ser Val Asp Gln Ser Val Leu Ala Ser Tyr Gln Thr Leu Gln
 20 25 30
 Pro Glu Leu Asn Ala Leu Leu Asn Ser Ala Pro Thr Pro Glu Met Leu
 35 40 45

Ser Ile Thr Ile Ser Asp Asp Ser Asp Ala Asn Ser Phe Glu Ser Gln
 50 55 60

Leu Asn Ala Ala Thr Asn Ala Ile Asn Asn Gly Tyr Ile Val Lys Leu
 65 70 75 80

Ala Thr Ala Thr His Ala Leu Leu Met Leu Pro Ala Leu Lys Ala Ala
 85 90 95

Gln Met Arg Ile His Pro His Ala Gln Leu Ala Ala Met Gln Gln Ala
 100 105 110

Lys Ser Thr Pro Met Ser Gln Val Ser Gly Glu Leu Lys Leu Gly Ala
 115 120 125

Asn Ala Leu Ser Leu Ala Gln Thr Asn Ala Leu Ser His Ala Leu Ser
 130 135 140

Gln Ala Lys Arg Asn Leu Thr Asp Val Ser Val Asn Glu Cys Phe Glu
 145 150 155 160

Asn Leu Lys Ser Glu Gln Gln Phe Thr Glu Val Tyr Ser Leu Ile Gln
 165 170 175

Gln Leu Ala Ser Arg Thr His Val Arg Lys Glu Val Asn Gln Gly Val
 180 185 190

Glu Leu Gly Pro Lys Gln Ala Lys Ser His Tyr Trp Phe Ser Glu Phe
 195 200 205

His Gln Asn Arg Val Ala Ala Ile Asn Phe Ile Asn Gly Gln Gln Ala
 210 215 220

Thr Ser Tyr Val Leu Thr Gln Gly Ser Gly Leu Leu Ala Ala Lys Ser
 225 230 235 240

Met Leu Asn Gln Gln Arg Leu Met Phe Ile Leu Pro Gly Asn Ser Gln
 245 250 255

Gln Gln Ile Thr Ala Ser Ile Thr Gln Leu Met Gln Gln Leu Glu Arg
 260 265 270

Leu Gln Val Thr Glu Val Asn Glu Leu Ser Leu Glu Cys Gln Leu Glu
 275 280 285

Leu Leu Ser Ile Met Tyr Asp Asn Leu Val Asn Ala Asp Lys Leu Thr
 290 295 300

Thr Arg Asp Ser Lys Pro Ala Tyr Gln Ala Val Ile Gln Ala Ser Ser			
305	310	315	320
Val Ser Ala Ala Lys Gln Glu Leu Ser Ala Leu Asn Asp Ala Leu Thr			
325	330		335
Ala Leu Phe Ala Glu Gln Thr Asn Ala Thr Ser Thr Asn Lys Gly Leu			
340	345		350
Ile Gln Tyr Lys Thr Pro Ala Gly Ser Tyr Leu Thr Leu Thr Pro Leu			
355	360		365
Gly Ser Asn Asn Asp Asn Ala Gln Ala Gly Leu Ala Phe Val Tyr Pro			
370	375		380
Gly Val Gly Thr Val Tyr Ala Asp Met Leu Asn Glu Leu His Gln Tyr			
385	390	395	400
Phe Pro Ala Leu Tyr Ala Lys Leu Glu Arg Glu Gly Asp Leu Lys Ala			
405	410		415
Met Leu Gln Ala Glu Asp Ile Tyr His Leu Asp Pro Lys His Ala Ala			
420	425		430
Gln Met Ser Leu Gly Asp Leu Ala Ile Ala Gly Val Gly Ser Ser Tyr			
435	440		445
Leu Leu Thr Gln Leu Leu Thr Asp Glu Phe Asn Ile Lys Pro Asn Phe			
450	455		460
Ala Leu Gly Tyr Ser Met Gly Glu Ala Ser Met Trp Ala Ser Leu Gly			
465	470	475	480
Val Trp Gln Asn Pro His Ala Leu Ile Ser Lys Thr Gln Thr Asp Pro			
485	490		495
Leu Phe Thr Ser Ala Ile Ser Gly Lys Leu Thr Ala Val Arg Gln Ala			
500	505		510
Trp Gln Leu Asp Asp Thr Ala Ala Glu Ile Gln Trp Asn Ser Phe Val			
515	520		525
Val Arg Ser Glu Ala Ala Pro Ile Glu Ala Leu Leu Lys Asp Tyr Pro			
530	535		540
His Ala Tyr Leu Ala Ile Ile Gln Gly Asp Thr Cys Val Ile Ala Gly			
545	550	555	560

Cys Glu Ile Gln Cys Lys Ala Leu Leu Ala Ala Leu Gly Lys Arg Gly
 565 570 575
 Ile Ala Ala Asn Arg Val Thr Ala Met His Thr Gln Pro Ala Met Gln
 580 585 590
 Glu His Gln Asn Val Met Asp Phe Tyr Leu Gln Pro Leu Lys Ala Glu
 595 600 605
 Leu Pro Ser Glu Ile Ser Phe Ile Ser Ala Ala Asp Leu Thr Ala Lys
 610 615 620
 Gln Thr Val Ser Glu Gln Ala Leu Ser Ser Gln Val Val Ala Gln Ser
 625 630 635 640
 Ile Ala Asp Thr Phe Cys Gln Thr Leu Asp Phe Thr Ala Leu Val His
 645 650 655
 His Ala Gln His Gln Gly Ala Lys Leu Phe Val Glu Ile Gly Ala Asp
 660 665 670
 Arg-Gln Asn Cys Thr Leu Ile Asp Lys Ile Val Lys Gln Asp Gly Ala
 675 680 685
 Ser Ser Val Gln His Gln Pro Cys Cys Thr Val Pro Met Asn Ala Lys
 690 695 700
 Gly Ser Gln Asp Ile Thr Ser Val Ile Lys Ala Leu Gly Gln Leu Ile
 705 710 715 720
 Ser His Gln Val Pro Leu Ser Val Gln Pro Phe Ile Asp Gly Leu Lys
 725 730 735
 Arg Glu Leu Thr Leu Cys Gln Leu Thr Ser Gln Gln Leu Ala Ala His
 740 745 750
 Ala Asn Val Asp Ser Lys Phe Glu Ser Asn Gln Asp His Leu Leu Gln
 755 760 765
 Gly Glu Val
 770

<210> 9

<211> 2004

<212> PRT

<213> Shewanella putrefaciens

<400> 9

Met Ser Leu Pro Asp Asn Ala Ser Asn His Leu Ser Ala Asn Gln Lys
 1 5 10 15

Gly Ala Ser Gln Ala Ser Lys Thr Ser Lys Gln Ser Lys Ile Ala Ile
 20 25 30

Val Gly Leu Ala Thr Leu Tyr Pro Asp Ala Lys Thr Pro Gln Glu Phe
 35 40 45

Trp Gln Asn Leu Leu Asp Lys Arg Asp Ser Arg Ser Thr Leu Thr Asn
 50 55 60

Glu Lys Leu Gly Ala Asn Ser Gln Asp Tyr Gln Gly Val Gln Gly Gln
 65 70 75 80

Ser Asp Arg Phe Tyr Cys Asn Lys Gly Gly Tyr Ile Glu Asn Phe Ser
 85 90 95

Phe Asn Ala Ala Gly Tyr Lys Leu Pro Glu Gln Ser Leu Asn Gly Leu
 100 105 110

Asp Asp Ser Phe Leu Trp Ala Leu Asp Thr Ser Arg Asn Ala Leu Ile
 115 120 125

Asp Ala Gly Ile Asp Ile Asn Gly Ala Asp Leu Ser Arg Ala Gly Val
 130 135 140

Val Met Gly Ala Leu Ser Phe Pro Thr Thr Arg Ser Asn Asp Leu Phe
 145 150 155 160

Leu Pro Ile Tyr His Ser Ala Val Glu Lys Ala Leu Gln Asp Lys Leu
 165 170 175

Gly Val Lys Ala Phe Lys Leu Ser Pro Thr Asn Ala His Thr Ala Arg
 180 185 190

Ala Ala Asn Glu Ser Ser Leu Asn Ala Ala Asn Gly Ala Ile Ala His
 195 200 205

Asn Ser Ser Lys Val Val Ala Asp Ala Leu Gly Leu Gly Gly Ala Gln
 210 215 220

Leu Ser Leu Asp Ala Ala Cys Ala Ser Ser Val Tyr Ser Leu Lys Leu
 225 230 235 240

Ala Cys Asp Tyr Leu Ser Thr Gly Lys Ala Asp Ile Met Leu Ala Gly
 245 250 255

Ala Val Ser Gly Ala Asp Pro Phe Phe Ile Asn Met Gly Phe Ser Ile
 260 265 270

Phe His Ala Tyr Pro Asp His Gly Ile Ser Val Pro Phe Asp Ala Ser
 275 280 285

Ser Lys Gly Leu Phe Ala Gly Glu Gly Ala Gly Val Leu Val Leu Lys
 290 295 300

Arg Leu Glu Asp Ala Glu Arg Asp Asn Asp Lys Ile Tyr Ala Val Val
 305 310 315 320

Ser Gly Val Gly Leu Ser Asn Asp Gly Lys Gly Gln Phe Val Leu Ser
 325 330 335

Pro Asn Pro Lys Gly Gln Val Lys Ala Phe Glu Arg Ala Tyr Ala Ala
 340 345 350

Ser Asp Ile Glu Pro Lys Asp Ile Glu Val Ile Glu Cys His Ala Thr
 355 360 365

Gly Thr Pro Leu Gly Asp Lys Ile Glu Leu Thr Ser Met Glu Thr Phe
 370 375 380

Phe Glu Asp Lys Leu Gln Gly Thr Asp Ala Pro Leu Ile Gly Ser Ala
 385 390 395 400

Lys Ser Asn Leu Gly His Leu Leu Thr Ala Ala His Ala Gly Ile Met
 405 410 415

Lys Met Ile Phe Ala Met Lys Glu Gly Tyr Leu Pro Pro Ser Ile Asn
 420 425 430

Ile Ser Asp Ala Ile Ala Ser Pro Lys Lys Leu Phe Gly Lys Pro Thr
 435 440 445

Leu Pro Ser Met Val Gln Gly Trp Pro Asp Lys Pro Ser Asn Asn His
 450 455 460

Phe Gly Val Arg Thr Arg His Ala Gly Val Ser Val Phe Gly Phe Gly
 465 470 475 480

Gly Cys Asn Ala His Leu Leu Leu Glu Ser Tyr Asn Gly Lys Gly Thr
 485 490 495

Val Lys Ala Glu Ala Thr Gln Val Pro Arg Gln Ala Glu Pro Leu Lys
 500 505 510

Val Val Gly Leu Ala Ser His Phe Gly Pro Leu Ser Ser Ile Asn Ala
 515 520 525

Leu Asn Asn Ala Val Thr Gln Asp Gly Asn Gly Phe Ile Glu Leu Pro
 530 535 540

Lys Lys Arg Trp Lys Gly Leu Glu Lys His Ser Glu Leu Leu Ala Glu
 545 550 555 560

Phe Gly Leu Ala Ser Ala Pro Lys Gly Ala Tyr Val Asp Asn Phe Glu
 565 570 575

Leu Asp Phe Leu Arg Phe Lys Leu Pro Pro Asn Glu Asp Asp Arg Leu
 580 585 590

Ile Ser Gln Gln Leu Met Leu Met Arg Val Thr Asp Glu Ala Ile Arg
 595 600 605

Asp Ala Lys Leu Glu Pro Gly Gln Lys Val Ala Val Leu Val Ala Met
 610 615 620

Glu Thr Glu Leu Glu Leu His Gln Phe Arg Gly Arg Val Asn Leu His
 625 630 635 640

Thr Gln Leu Ala Gln Ser Leu Ala Ala Met Gly Val Ser Leu Ser Thr
 645 650 655

Asp Glu Tyr Gln Ala Leu Glu Ala Ile Ala Met Asp Ser Val Leu Asp
 660 665 670

Ala Ala Lys Leu Asn Gln Tyr Thr Ser Phe Ile Gly Asn Ile Met Ala
 675 680 685

Ser Arg Val Ala Ser Leu Trp Asp Phe Asn Gly Pro Ala Phe Thr Ile
 690 695 700

Ser Ala Ala Glu Gln Ser Val Ser Arg Cys Ile Asp Val Ala Gln Asn
 705 710 715 720

Leu Ile Met Glu Asp Asn Leu Asp Ala Val Val Ile Ala Ala Val Asp
 725 730 735

Leu Ser Gly Ser Phe Glu Gln Val Ile Leu Lys Asn Ala Ile Ala Pro
 740 745 750

Val Ala Ile Glu Pro Asn Leu Glu Ala Ser Leu Asn Pro Thr Ser Ala
 755 760 765

Ser Trp Asn Val Gly Glu Gly Ala Gly Ala Val Val Leu Val Lys Asn
 770 775 780

Glu Ala Thr Ser Gly Cys Ser Tyr Gly Gln Ile Asp Ala Leu Gly Phe
 785 790 795 800

Ala Lys Thr Ala Glu Thr Ala Leu Ala Thr Asp Lys Leu Leu Ser Gln
 805 810 815

Thr Ala Thr Asp Phe Asn Lys Val Lys Val Ile Glu Thr Met Ala Ala
 820 825 830

Pro Ala Ser Gln Ile Gln Leu Ala Pro Ile Val Ser Ser Gln Val Thr
 835 840 845

His Thr Ala Ala Glu Gln Arg Val Gly His Cys Phe Ala Ala Ala Gly
 850 855 860

Met Ala Ser Leu Leu His Gly Leu Leu Asn Leu Asn Thr Val Ala Gln
 865 870 875 880

Thr Asn Lys Ala Asn Cys Ala Leu Ile Asn Asn Ile Ser Glu Asn Gln
 885 890 895

Leu Ser Gln Leu Leu Ile Ser Gln Thr Ala Ser Glu Gln Gln Ala Leu
 900 905 910

Thr Ala Arg Leu Ser Asn Glu Leu Lys Ser Asp Ala Lys His Gln Leu
 915 920 925

Val Lys Gln Val Thr Leu Gly Gly Arg Asp Ile Tyr Gln His Ile Val
 930 935 940

Asp Thr Pro Leu Ala Ser Leu Glu Ser Ile Thr Gln Lys Leu Ala Gln
 945 950 955 960

Ala Thr Ala Ser Thr Val Val Asn Gln Val Lys Pro Ile Lys Ala Ala
 965 970 975

Gly Ser Val Glu Met Ala Asn Ser Phe Glu Thr Glu Ser Ser Ala Glu
 980 985 990

Pro Gln Ile Thr Ile Ala Ala Gln Gln Thr Ala Asn Ile Gly Val Thr
 995 1000 1005

Ala Gln Ala Thr Lys Arg Glu Leu Gly Thr Pro Pro Met Thr Thr Asn
 1010 1015 1020

Thr Ile Ala Asn Thr Ala Asn Asn Leu Asp Lys Thr Leu Glu Thr Val
 1025 1030 1035 1040

Ala Gly Asn Thr Val Ala Ser Lys Val Gly Ser Gly Asp Ile Val Asn
 1045 1050 1055

Phe Gln Gln Asn Gln Gln Leu Ala Gln Gln Ala His Leu Ala Phe Leu
 1060 1065 1070

Glu Ser Arg Ser Ala Gly Met Lys Val Ala Asp Ala Leu Leu Lys Gln
 1075 1080 1085

Gln Leu Ala Gln Val Thr Gly Gln Thr Ile Asp Asn Gln Ala Leu Asp
 1090 1095 1100

Thr Gln Ala Val Asp Thr Gln Thr Ser Glu Asn Val Ala Ile Ala Ala
 1105 1110 1115 1120

Glu Ser Pro Val Gln Val Thr Thr Pro Val Gln Val Thr Thr Pro Val
 1125 1130 1135

Gln Ile Ser Val Val Glu Leu Lys Pro Asp His Ala Asn Val Pro Pro
 1140 1145 1150

Tyr Thr Pro Pro Val Pro Ala Leu Lys Pro Cys Ile Trp Asn Tyr Ala
 1155 1160 1165

Asp Leu Val Glu Tyr Ala Glu Gly Asp Ile Ala Lys Val Phe Gly Ser
 1170 1175 1180

Asp Tyr Ala Ile Ile Asp Ser Tyr Ser Arg Arg Val Arg Leu Pro Thr
 1185 1190 1195 1200

Thr Asp Tyr Leu Leu Val Ser Arg Val Thr Lys Leu Asp Ala Thr Ile
 1205 1210 1215

Asn Gln Phe Lys Pro Cys Ser Met Thr Thr Glu Tyr Asp Ile Pro Val
 1220 1225 1230

Asp Ala Pro Tyr Leu Val Asp Gly Gln Ile Pro Trp Ala Val Ala Val
 1235 1240 1245

Glu Ser Gly Gln Cys Asp Leu Met Leu Ile Ser Tyr Leu Gly Ile Asp
 1250 1255 1260

Phe Glu Asn Lys Gly Glu Arg Val Tyr Arg Leu Leu Asp Cys Thr Leu
 1265 1270 1275 1280

Thr Phe Leu Gly Asp Leu Pro Arg Gly Gly Asp Thr Leu Arg Tyr Asp
 1285 1290 1295

Ile Lys Ile Asn Asn Tyr Ala Arg Asn Gly Asp Thr Leu Leu Phe Phe
 1300 1305 1310

Phe Ser Tyr Glu Cys Phe Val Gly Asp Lys Met Ile Leu Lys Met Asp
 1315 1320 1325

Gly Gly Cys Ala Gly Phe Phe Thr Asp Glu Glu Leu Ala Asp Gly Lys
 1330 1335 1340

Gly Val Ile Arg Thr Glu Glu Glu Ile Lys Ala Arg Ser Leu Val Gln
 1345 1350 1355 1360

Lys Gln Arg Phe Asn Pro Leu Leu Asp Cys Pro Lys Thr Gln Phe Ser
 1365 1370 1375

Tyr Gly Asp Ile His Lys Leu Leu Thr Ala Asp Ile Glu Gly Cys Phe
 1380 1385 1390

Gly Pro Ser His Ser Gly Val His Gln Pro Ser Leu Cys Phe Ala Ser
 1395 1400 1405

Glu Lys Phe Leu Met Ile Glu Gln Val Ser Lys Val Asp Arg Thr Gly
 1410 1415 1420

Gly Thr Trp Gly Leu Gly Leu Ile Glu Gly His Lys Gln Leu Glu Ala
 1425 1430 1435 1440

Asp His Trp Tyr Phe Pro Cys His Phe Lys Gly Asp Gln Val Met Ala
 1445 1450 1455

Gly Ser Leu Met Ala Glu Gly Cys Gly Gln Leu Leu Gln Phe Tyr Met
 1460 1465 1470

Leu His Leu Gly Met His Thr Gln Thr Lys Asn Gly Arg Phe Gln Pro
 1475 1480 1485

Leu Glu Asn Ala Ser Gln Gln Val Arg Cys Arg Gly Gln Val Leu Pro
 1490 1495 1500

Gln Ser Gly Val Leu Thr Tyr Arg Met Glu Val Thr Glu Ile Gly Phe
 1505 1510 1515 1520

Ser Pro Arg Pro Tyr Ala Lys Ala Asn Ile Asp Ile Leu Leu Asn Gly
 1525 1530 1535

Lys Ala Val Val Asp Phe Gln Asn Leu Gly Val Met Ile Lys Glu Glu
 1540 1545 1550

Asp Glu Cys Thr Arg Tyr Pro Leu Leu Thr Glu Ser Thr Thr Ala Ser
 1555 1560 1565

Thr Ala Gln Val Asn Ala Gln Thr Ser Ala Lys Lys Val Tyr Lys Pro
 1570 1575 1580

Ala Ser Val Asn Ala Pro Leu Met Ala Gln Ile Pro Asp Leu Thr Lys
 1585 1590 1595 1600

Glu Pro Asn Lys Gly Val Ile Pro Ile Ser His Val Glu Ala Pro Ile
 1605 1610 1615

Thr Pro Asp Tyr Pro Asn Arg Val Pro Asp Thr Val Pro Phe Thr Pro
 1620 1625 1630

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Gly Tyr Met Gly Thr Thr Leu Gly Phe Pro Gly Leu Glu Leu Phe Phe
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Gly Thr Asn Ile Ile Gln Ser Phe Ser Phe Glu Leu Ser Thr Asp Gly
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Glu Pro Phe Tyr Arg Gly Thr Ala Val Phe Gly Tyr Phe Lys Gly Asp
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Trp His Val Ala Asn Gly Val Ala Ala Ser Thr Lys Val Asn Leu Leu
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Asp Lys Ser Cys Arg His Phe Asn Ala Pro Ala Asn Gln Pro His Tyr
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Arg Leu Ala Gly Gly Gln Leu Asn Phe Ile Asp Ser Val Glu Ile Val
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Asp Asn Gly Gly Thr Glu Gly Leu Gly Tyr Leu Tyr Ala Glu Arg Thr
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Ile Asp Pro Ser Asp Trp Phe Phe Gln Phe His Phe His Gln Asp Pro
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Val Met Pro Gly Ser Leu Gly Val Glu Ala Ile Ile Glu Thr Met Gln
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Ala Tyr Ala Ile Ser Lys Asp Leu Gly Ala Asp Phe Lys Asn Pro Lys
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<213> *Shewanella putrefaciens*

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Ile Gln Glu Cys Asp Asn Gln Thr Thr Glu Leu Val Lys Ser Trp Leu
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Pro Glu Asp Glu Leu Ile Lys Val Asn Arg Tyr Ile Lys Gln Glu Ala
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<213> *Shewanella putrefaciens*

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<211> 28

<212> DNA

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<223> Description of Artificial Sequence: SYNTHETIC

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<210> 27

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<223> Description of Artificial Sequence: SYNTHETIC

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<210> 28

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<223> Description of Artificial Sequence: SYNTHETIC

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29

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<211> 29

<212> DNA

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<223> Description of Artificial Sequence: SYNTHETIC

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29

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<211> 98

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: SYNTHETIC

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cgcgccgcgc gggtagtagc tcatttggtt ttggtggc 98

<210> 31

<211> 98

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: SYNTHETIC

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cacgtcgtgc aggtattagc tcatttggtt ttggtggc 98

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<213> *Shewanella putrefaciens*

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<210> 33
<211> 4
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<400> 33
Gly Phe Gly Gly
1

<210> 34
<211> 5
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<213> *Shewanella putrefaciens*

<400> 34
Gly His Ser Xaa Gly
1 5

<210> 35
<211> 6
<212> PRT
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<400> 35
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1 5

<210> 36
<211> 6
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<400> 36
Leu Gly Xaa Asp Ser Ile
1 5

<210> 37
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<212> PRT
<213> *Shewanella putrefaciens*

<400> 37
Gly Xaa Gly Xaa Xaa Gly
1 5

<210> 38
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<213> *Shewanella putrefaciens*

<400> 38
Gly Xaa Gly Xaa Xaa Ala
1 5

<210> 39
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<213> 'Axial Seamount' polynoid polychaete

<400> 39
Gly Xaa Gly Xaa Xaa Pro
1 5

<210> 40
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<213> *Shewanella putrefaciens*

<400> 40
Gly Xaa Ser Xaa Gly
1 5

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cuacuacuac uaccaagcta aagcacttaa ccgtg 35

<210> 42
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<210> 43
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<210> 45
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<220>
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<210> 46

<211> 56

<212> DNA

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<223> Description of Artificial Sequence: synthetic

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<210> 47

<211> 41

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic

<400> 47

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<210> 48

<211> 37

<212> DNA

<213> Artificial Sequence

<220>

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<210> 49

<211> 39

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic

<400> 49

tctagactcg agacaatgag ccagacctct aaacctaca 39

<210> 50

<211> 37

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic

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37

<210> 51

<211> 39

<212> DNA

<213> Artificial Sequence

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<400> 51

gaattctctg agacaatgcc gctgcgcac gcacttatc

39

<210> 52

<211> 37

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37

<210> 53

<211> 39

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<210> 54

<211> 38

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<400> 54
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<210> 55
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<400> 56
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<210> 57
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<400> 57
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<210> 58
<211> 36
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<223> Description of Artificial Sequence: synthetic

<400> 58
gtcgacggat ccctatttgt tcgtgtttgc tatatg 36

<210> 59

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<210> 60

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<210> 61

<211> 39

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<223> Description of Artificial Sequence: synthetic

<400> 61

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<210> 62

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic

<400> 62

cccgggtcga ctcatgacat atcgttcaaa atgtcactga

40

<210> 63

<211> 44

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic

<400> 63

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44

<210> 64

<211> 44

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic

<400> 64

ccgggaacaa attagcaata cctactactg caatattttc catg

44

<210> 65

<211> 21

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic

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<210> 66

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic

<400> 66

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36

<210> 67

<211> 30

<212> DNA

<213> Schizochytrium aggregatum

<400> 67

gtgatgatct ttccctgatg cacgcccaagg

30

<210> 68

<211> 30

<212> DNA

<213> Schizochytrium aggregatum

<400> 68

agctcgagac cggcaacccg cagcgccaga

30

<210> 69

<211> 4446

<212> DNA

<213> Schizochytrium aggregatum

<400> 69

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<211> 1481

<212> PRT

<213> Schizochytrium aggregatum

<400> 70.

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35	40	45	
Gly Tyr Glu Thr Asp Met Ile Glu Ser Asp Met Glu Leu Glu Thr Glu			
50	55	60	
Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val Gln			
65	70	75	80
Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg Thr			
85	90	95	
Arg Thr Val Gly Glu Val Val Asn Ala Met Lys Ala Glu Ile Ala Gly			
100	105	110	
Gly Ser Ala Pro Ala Pro Ala Ala Ala Ala Pro Gly Pro Ala Ala Ala			
115	120	125	
Ala Pro Ala Pro Ala Val Ser Ser Glu Leu Leu Glu Lys Ala Glu Thr			
130	135	140	
Val Val Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met			
145	150	155	160
Ile Glu Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile			
165	170	175	
Lys Arg Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu			
180	185	190	
Ala Lys Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val			
195	200	205	
Val Asp Ala Met Lys Ala Glu Ile Ala Gly Ser Ser Ala Ser Ala Pro			
210	215	220	
Ala Ala Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Pro Ala Ala			
225	230	235	240
Ala Ala Pro Ala Val Ser Asn Glu Leu Leu Glu Lys Ala Glu Thr Val			
245	250	255	
Val Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met Ile			

260	265	270
Glu Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile Lys		
275	280	285
Arg Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu Ala		
290	295	300
Lys Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val Val		
305	310	315 320
Asp Ala Met Lys Ala Glu Ile Ala Gly Gly Ser Ala Pro Ala Pro Ala		
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Ala Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Val Ser Asn Glu		
340	345	350
Leu Leu Glu Lys Ala Glu Thr Val Val Met Glu Val Leu Ala Ala Lys		
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Thr Gly Tyr Glu Thr Asp Met Ile Glu Ser Asp Met Glu Leu Glu Thr		
370	375	380
Glu Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val		
385	390	395 400
Gln Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg		
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Thr Arg Thr Val Gly Glu Val Val Asp Ala Met Lys Ala Glu Ile Ala		
420	425	430
Gly Ser Ser Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Pro Ala Ala		
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Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Val Ser Ser Glu Leu		
450	455	460
Leu Glu Lys Ala Glu Thr Val Val Met Glu Val Leu Ala Ala Lys Thr		
465	470	475 480
Gly Tyr Glu Thr Asp Met Ile Glu Ser Asp Met Glu Leu Glu Thr Glu		
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Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val Gln		
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Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg Thr		

515	520	525
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530	535	540
Gly Ser Ala Pro Ala Pro Ala Ala Ala Pro Ala Pro Ala Ala Ala		
545	550	555 560
Ala Pro Ala Val Ser Asn Glu Leu Leu Glu Lys Ala Glu Thr Val Val		
565	570	575
Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met Ile Glu		
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Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile Lys Arg		
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Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu Ala Lys		
610	615	620
Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val Val Asp		
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Ala Met Lys Ala Glu Ile Ala Gly Gly Ser Ala Pro Ala Pro Ala Ala		
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Ala Ala Pro Ala Ser Ala Gly Ala Ala Pro Ala Val Lys Ile Asp Ser		
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Val His Gly Ala Asp Cys Asp Asp Leu Ser Leu Met His Ala Lys Val		
675	680	685
Val Asp Ile Arg Arg Pro Asp Glu Leu Ile Leu Glu Arg Pro Glu Asn		
690	695	700
Arg Pro Val Leu Val Val Asp Asp Gly Ser Glu Leu Thr Leu Ala Leu		
705	710	715 720
Val Arg Val Leu Gly Ala Cys Ala Val Val Leu Thr Phe Glu Gly Leu		
725	730	735
Gln Leu Ala Gln Arg Ala Gly Ala Ala Ala Ile Arg His Val Leu Ala		
740	745	750
Lys Asp Leu Ser Ala Glu Ser Ala Glu Lys Ala Ile Lys Glu Ala Glu		
755	760	765
Gln Arg Phe Gly Ala Leu Gly Gly Phe Ile Ser Gln Gln Ala Glu Arg		

770	775	780
Phe Glu Pro Ala Glu Ile Leu Gly Phe Thr Leu Met Cys Ala Lys Phe		
785	790	795 800
Ala Lys Ala Ser Leu Cys Thr Ala Val Ala Gly Gly Arg Pro Ala Phe		
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Ile Gly Val Ala Arg Leu Asp Gly Arg Leu Gly Phe Thr Ser Gln Gly		
	820	825 830
Thr Ser Asp Ala Leu Lys Arg Ala Gln Arg Gly Ala Ile Phe Gly Leu		
	835	840 845
Cys Lys Thr Ile Gly Leu Glu Trp Ser Glu Ser Asp Val Phe Ser Arg		
	850	855 860
Gly Val Asp Ile Ala Gln Gly Met His Pro Glu Asp Ala Ala Val Ala		
865	870	875 880
Ile Val Arg Glu Met Ala Cys Ala Asp Ile Arg Ile Arg Glu Val Gly		
	885	890 895
Ile Gly Ala Asn Gln Gln Arg Cys Thr Ile Arg Ala Ala Lys Leu Glu		
	900	905 910
Thr Gly Asn Pro Gln Arg Gln Ile Ala Lys Asp Asp Val Leu Leu Val		
	915	920 925
Ser Gly Gly Ala Arg Gly Ile Thr Pro Leu Cys Ile Arg Glu Ile Thr		
	930	935 940
Arg Gln Ile Ala Gly Gly Lys Tyr Ile Leu Leu Gly Arg Ser Lys Val		
945	950	955 960
Ser Ala Ser Glu Pro Ala Trp Cys Ala Gly Ile Thr Asp Glu Lys Ala		
	965	970 975
Val Gln Lys Ala Ala Thr Gln Glu Leu Lys Arg Ala Phe Ser Ala Gly		
	980	985 990
Glu Gly Pro Lys Pro Thr Pro Arg Ala Val Thr Lys Leu Val Gly Ser		
	995	1000 1005
Val Leu Gly Ala Arg Glu Val Arg Ser Ser Ile Ala Ala Ile Glu Ala		
1010	1015	1020
Leu Gly Gly Lys Ala Ile Tyr Ser Ser Cys Asp Val Asn Ser Ala Ala		

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	1045	1050	1055
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	1060	1065	1070
Glu Lys Lys Leu Pro Asp Glu Phe Asp Ala Val Phe Gly Thr Lys Val			
	1075	1080	1085
Thr Gly Leu Glu Asn Leu Leu Ala Ala Val Asp Arg Ala Asn Leu Lys			
	1090	1095	1100
His Met Val Leu Phe Ser Ser Leu Ala Gly Phe His Gly Asn Val Gly			
	1105	1110	1115
Gln Ser Asp Tyr Ala Met Ala Asn Glu Ala Leu Asn Lys Met Gly Leu			
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Ile Ser Ala Lys Ser Asn Pro Phe Leu Glu Asp His Val Ile Gln Gly			
	1220	1225	1230
Arg Arg Val Leu Pro Met Thr Leu Ala Ile Gly Ser Leu Ala Glu Thr			
	1235	1240	1245
Cys Leu Gly Leu Phe Pro Gly Tyr Ser Leu Trp Ala Ile Asp Asp Ala			
	1250	1255	1260
Gln Leu Phe Lys Gly Val Thr Val Asp Gly Asp Val Asn Cys Glu Val			
	1265	1270	1275
Thr Leu Thr Pro Ser Thr Ala Pro Ser Gly Arg Val Asn Val Gln Ala			

	1285	1290	1295
Thr Leu Lys Thr Phe Ser Ser Gly Lys Leu Val Pro Ala Tyr Arg Ala	1300	1305	1310
Val Ile Val Leu Ser Asn Gln Gly Ala Pro Pro Ala Asn Ala Thr Met	1315	1320	1325
Gln Pro Pro Ser Leu Asp Ala Asp Pro Ala Leu Gln Gly Ser Val Tyr	1330	1335	1340
Asp Gly Lys Thr Leu Phe His Gly Pro Ala Phe Arg Gly Ile Asp Asp	1345	1350	1355 1360
Val Leu Ser Cys Thr Lys Ser Gln Leu Val Ala Lys Cys Ser Ala Val	1365	1370	1375
Pro Gly Ser Asp Ala Ala Arg Gly Glu Phe Ala Thr Asp Thr Asp Ala	1380	1385	1390
His Asp Pro Phe Val Asn Asp Leu Ala Phe Gln Ala Met Leu Val Trp	1395	1400	1405
Val Arg Arg Thr Leu Gly Gln Ala Ala Leu Pro Asn Ser Ile Gln Arg	1410	1415	1420
Ile Val Gln His Arg Pro Val Pro Gln Asp Lys Pro Phe Tyr Ile Thr	1425	1430	1435 1440
Leu Arg Ser Asn Gln Ser Gly Gly His Ser Gln His Lys His Ala Leu	1445	1450	1455
Gln Phe His Asn Glu Gln Gly Asp Leu Phe Ile Asp Val Gln Ala Ser	1460	1465	1470
Val Ile Ala Thr Asp Ser Leu Ala Phe	1475	1480	

<210> 71

<211> 5215

<212> DNA

<213> Schizochytrium aggregatum

<400> 71

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<210> 72

<211> 1622

<212> PRT

<213> Schizochytrium aggregatum

<400> 72

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25

30

Arg Ile Ala Ile Thr Gly Met Asp Ala Thr Phe Gly Ala Leu Lys Gly
 35 40 45

Leu Asp Ala Phe Glu Arg Ala Ile Tyr Thr Gly Ala His Gly Ala Ile
 50 55 60

Pro Leu Pro Glu Lys Arg Trp Arg Phe Leu Gly Lys Asp Lys Asp Phe
 65 70 75 80

Leu Asp Leu Cys Gly Val Lys Ala Thr Pro His Gly Cys Tyr Ile Glu
 85 90 95

Asp Val Glu Val Asp Phe Gln Arg Leu Arg Thr Pro Met Thr Pro Glu
 100 105 110

Asp Met Leu Leu Pro Gln Gln Leu Leu Ala Val Thr Thr Ile Asp Arg
 115 120 125

Ala Ile Leu Asp Ser Gly Met Lys Lys Gly Gly Asn Val Ala Val Phe
 130 135 140

Val Gly Leu Gly Thr Asp Leu Glu Leu Tyr Arg His Arg Ala Arg Val
 145 150 155 160

Ala Leu Lys Glu Arg Val Arg Pro Glu Ala Ser Lys Lys Leu Asn Asp
 165 170 175

Met Met Gln Tyr Ile Asn Asp Cys Gly Thr Ser Thr Ser Tyr Thr Ser
 180 185 190

Tyr Ile Gly Asn Leu Val Ala Thr Arg Val Ser Ser Gln Trp Gly Phe
 195 200 205

Thr Gly Pro Ser Phe Thr Ile Thr Glu Gly Asn Asn Ser Val Tyr Arg
 210 215 220

Cys Ala Glu Leu Gly Lys Tyr Leu Leu Glu Thr Gly Glu Val Asp Gly
 225 230 235 240

Val Val Val Ala Gly Val Asp Leu Cys Gly Ser Ala Glu Asn Leu Tyr
 245 250 255

Val Lys Ser Arg Arg Phe Lys Val Ser Thr Ser Asp Thr Pro Arg Ala
 260 265 270

Ser Phe Asp Ala Ala Ala Asp Gly Tyr Phe Val Gly Glu Gly Cys Gly
 275 280 285

Ala Phe Val Leu Lys Arg Glu Thr Ser Cys Thr Lys Asp Asp Arg Ile
 290 295 300
 Tyr Ala Cys Met Asp Ala Ile Val Pro Gly Asn Val Pro Ser Ala Cys
 305 310 315 320
 Leu Arg Glu Ala Leu Asp Gln Ala Arg Val Lys Pro Gly Asp Ile Glu
 325 330 335
 Met Leu Glu Leu Ser Ala Asp Ser Ala Arg His Leu Lys Asp Pro Ser
 340 345 350
 Val Leu Pro Lys Glu Leu Thr Ala Glu Glu Glu Ile Gly Gly Leu Gln
 355 360 365
 Thr Ile Leu Arg Asp Asp Asp Lys Leu Pro Arg Asn Val Ala Thr Gly
 370 375 380
 Ser Val Lys Ala Thr Val Gly Asp Thr Gly Tyr Ala Ser Gly Ala Ala
 385 390 395 400
 Ser Leu Ile Lys Ala Ala Leu Cys Ile Tyr Asn Arg Tyr Leu Pro Ser
 405 410 415
 Asn Gly Asp Asp Trp Asp Glu Pro Ala Pro Glu Ala Pro Trp Asp Ser
 420 425 430
 Thr Leu Phe Ala Cys Gln Thr Ser Arg Ala Trp Leu Lys Asn Pro Gly
 435 440 445
 Glu Arg Arg Tyr Ala Ala Val Ser Gly Val Ser Glu Thr Arg Ser Cys
 450 455 460
 Tyr Ser Val Leu Leu Ser Glu Ala Glu Gly His Tyr Glu Arg Glu Asn
 465 470 475 480
 Arg Ile Ser Leu Asp Glu Glu Ala Pro Lys Leu Ile Val Leu Arg Ala
 485 490 495
 Asp Ser His Glu Glu Ile Leu Gly Arg Leu Asp Lys Ile Arg Glu Arg
 500 505 510
 Phe Leu Gln Pro Thr Gly Ala Ala Pro Arg Glu Ser Glu Leu Lys Ala
 515 520 525
 Gln Ala Arg Arg Ile Phe Leu Glu Leu Leu Gly Glu Thr Leu Ala Gln
 530 535 540

Asp Ala Ala Ser Ser Gly Ser Gln Lys Pro Leu Ala Leu Ser Leu Val
 545 550 555 560
 Ser Thr Pro Ser Lys Leu Gln Arg Glu Val Glu Leu Ala Ala Lys Gly
 565 570 575
 Ile Pro Arg Cys Leu Lys Met Arg Arg Asp Trp Ser Ser Pro Ala Gly
 580 585 590
 Ser Arg Tyr Ala Pro Glu Pro Leu Ala Ser Asp Arg Val Ala Phe Met
 595 600 605
 Tyr Gly Glu Gly Arg Ser Pro Tyr Tyr Gly Ile Thr Gln Asp Ile His
 610 615 620
 Arg Ile Trp Pro Glu Leu His Glu Val Ile Asn Glu Lys Thr Asn Arg
 625 630 635 640
 Leu Trp Ala Glu Gly Asp Arg Trp Val Met Pro Arg Ala Ser Phe Lys
 645 650 655
 Ser Glu Leu Glu Ser Gln Gln Gln Glu Phe Asp Arg Asn Met Ile Glu
 660 665 670
 Met Phe Arg Leu Gly Ile Leu Thr Ser Ile Ala Phe Thr Asn Leu Ala
 675 680 685
 Arg Asp Val Leu Asn Ile Thr Pro Lys Ala Ala Phe Gly Leu Ser Leu
 690 695 700
 Gly Glu Ile Ser Met Ile Phe Ala Phe Ser Lys Lys Asn Gly Leu Ile
 705 710 715 720
 Ser Asp Gln Leu Thr Lys Asp Leu Arg Glu Ser Asp Val Trp Asn Lys
 725 730 735
 Ala Leu Ala Val Glu Phe Asn Ala Leu Arg Glu Ala Trp Gly Ile Pro
 740 745 750
 Gln Ser Val Pro Lys Asp Glu Phe Trp Gln Gly Tyr Ile Val Arg Gly
 755 760 765
 Thr Lys Gln Asp Ile Glu Ala Ala Ile Ala Pro Asp Ser Lys Tyr Val
 770 775 780
 Arg Leu Thr Ile Ile Asn Asp Ala Asn Thr Ala Leu Ile Ser Gly Lys
 785 790 795 800

Pro Asp Ala Cys Lys Ala Ala Ile Ala Arg Leu Gly Gly Asn Ile Pro
 805 810 815

Ala Leu Pro Val Thr Gln Gly Met Cys Gly His Cys Pro Glu Val Gly
 820 825 830

Pro Tyr Thr Lys Asp Ile Ala Lys Ile His Ala Asn Leu Glu Phe Pro
 835 840 845

Val Val Asp Gly Leu Asp Leu Trp Thr Thr Ile Asn Gln Lys Arg Leu
 850 855 860

Val Pro Arg Ala Thr Gly Ala Lys Asp Glu Trp Ala Pro Ser Ser Phe
 865 870 875 880

Gly Glu Tyr Ala Gly Gln Leu Tyr Glu Lys Gln Ala Asn Phe Pro Gln
 885 890 895

Ile Val Glu Thr Ile Tyr Lys Gln Asn Tyr Asp Val Phe Val Glu Val
 900 905 910

Gly Pro Asn Asn His Arg Ser Thr Ala Val Arg Thr Thr Leu Gly Pro
 915 920 925

Gln Arg Asn His Leu Ala Gly Ala Ile Asp Lys Gln Asn Glu Asp Ala
 930 935 940

Trp Thr Thr Ile Val Lys Leu Val Ala Ser Leu Lys Ala His Leu Val
 945 950 955 960

Pro Gly Val Thr Ile Ser Pro Leu Tyr His Ser Lys Leu Val Ala Glu
 965 970 975

Ala Gln Ala Cys Tyr Ala Ala Leu Cys Lys Gly Glu Lys Pro Lys Lys
 980 985 990

Asn Lys Phe Val Arg Lys Ile Gln Leu Asn Gly Arg Phe Asn Ser Lys
 995 1000 1005

Ala Asp Pro Ile Ser Ser Ala Asp Leu Ala Ser Phe Pro Pro Ala Asp
 1010 1015 1020

Pro Ala Ile Glu Ala Ala Ile Ser Ser Arg Ile Met Lys Pro Val Ala
 1025 1030 1035 1040

Pro Lys Phe Tyr Ala Arg Leu Asn Ile Asp Glu Gln Asp Glu Thr Arg
 1045 1050 1055

Asp Pro Ile Leu Asn Lys Asp Asn Ala Pro Ser Ser Ser Ser Ser Ser
 1060 1065 1070

Ser Ser Ser Ser Ser Ser Ser Ser Ser Pro Ser Pro Ala Pro Ser Ala
 1075 1080 1085

Pro Val Gln Lys Lys Ala Ala Pro Ala Ala Glu Thr Lys Ala Val Ala
 1090 1095 1100

Ser Ala Asp Ala Leu Arg Ser Ala Leu Leu Asp Leu Asp Ser Met Leu
 1105 1110 1115 1120

Ala Leu Ser Ser Ala Ser Ala Ser Gly Asn Leu Val Glu Thr Ala Pro
 1125 1130 1135

Ser Asp Ala Ser Val Ile Val Pro Pro Cys Asn Ile Ala Asp Leu Gly
 1140 1145 1150

Ser Arg Ala Phe Met Lys Thr Tyr Gly Val Ser Ala Pro Leu Tyr Thr
 1155 1160 1165

Gly Ala Met Ala Lys Gly Ile Ala Ser Ala Asp Leu Val Ile Ala Ala
 1170 1175 1180

Gly Arg Gln Gly Ile Leu Ala Ser Phe Gly Ala Gly Gly Leu Pro Met
 1185 1190 1195 1200

Gln Val Val Arg Glu Ser Ile Glu Lys Ile Gln Ala Ala Leu Pro Asn
 1205 1210 1215

Gly Pro Tyr Ala Val Asn Leu Ile His Ser Pro Phe Asp Ser Asn Leu
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Glu Lys Gly Asn Val Asp Leu Phe Leu Glu Lys Gly Val Thr Phe Val
 1235 1240 1245

Glu Ala Ser Ala Phe Met Thr Leu Thr Pro Gln Val Val Arg Tyr Arg
 1250 1255 1260

Ala Ala Gly Leu Thr Arg Asn Ala Asp Gly Ser Val Asn Ile Arg Asn
 1265 1270 1275 1280

Arg Ile Ile Gly Lys Val Ser Arg Thr Glu Leu Ala Glu Met Phe Met
 1285 1290 1295

Arg Pro Ala Pro Glu His Leu Leu Gln Lys Leu Ile Ala Ser Gly Glu
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Ile Asn Gln Glu Gln Ala Glu Leu Ala Arg Arg Val Pro Val Ala Asp
 1315 1320 1325

Asp Ile Ala Val Glu Ala Asp Ser Gly Gly His Thr Asp Asn Arg Pro
 1330 1335 1340

Ile His Val Ile Leu Pro Leu Ile Ile Asn Leu Arg Asp Arg Leu His
 1345 1350 1355 1360

Arg Glu Cys Gly Tyr Pro Ala Asn Leu Arg Val Arg Val Gly Ala Gly
 1365 1370 1375

Gly Gly Ile Gly Cys Pro Gln Ala Ala Leu Ala Thr Phe Asn Met Gly
 1380 1385 1390

Ala Ser Phe Ile Val Thr Gly Thr Val Asn Gln Val Ala Lys Gln Ser
 1395 1400 1405

Gly Thr Cys Asp Asn Val Arg Lys Gln Leu Ala Lys Ala Thr Tyr Ser
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Asp Val Cys Met Ala Pro Ala Ala Asp Met Phe Glu Glu Gly Val Lys
 1425 1430 1435 1440

Leu Gln Val Leu Lys Lys Gly Thr Met Phe Pro Ser Arg Ala Asn Lys
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Leu Tyr Glu Leu Phe Cys Lys Tyr Asp Ser Phe Glu Ser Met Pro Pro
 1460 1465 1470

Ala Glu Leu Ala Arg Val Glu Lys Arg Ile Phe Ser Arg Ala Leu Glu
 1475 1480 1485

Glu Val Trp Asp Glu Thr Lys Asn Phe Tyr Ile Asn Arg Leu His Asn
 1490 1495 1500

Pro Glu Lys Ile Gln Arg Ala Glu Arg Asp Pro Lys Leu Lys Met Ser
 1505 1510 1515 1520

Leu Cys Phe Arg Trp Tyr Leu Ser Leu Ala Ser Arg Trp Ala Asn Thr
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Gly Ala Ser Asp Arg Val Met Asp Tyr Gln Val Trp Cys Gly Pro Ala
 1540 1545 1550

Ile Gly Ser Phe Asn Asp Phe Ile Lys Gly Thr Tyr Leu Asp Pro Ala
 1555 1560 1565

Val Ala Asn Glu Tyr Pro Cys Val Val Gln Ile Asn Lys Gln Ile Leu
 1570 1575 1580

Arg Gly Ala Cys Phe Leu Arg Arg Leu Glu Ile Leu Arg Asn Ala Arg
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Leu Ser Asp Gly Ala Ala Ala Leu Val Ala Ser Ile Asp Asp Thr Tyr
 1605 1610 1615

Val Pro Ala Glu Lys Leu
 1620

<210> 73

<211> 1551

<212> PRT

<213> Schizochytrium aggregatum

<400> 73

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Gln Gln Gln Gln Pro Arg Glu Gly Asp Lys Glu Lys Ala Ala Glu Thr
 35 40 45

Met Ala Leu Arg Val Lys Thr Asn Lys Lys Pro Cys Trp Glu Met Thr
 50 55 60

Lys Glu Glu Leu Thr Ser Gly Lys Thr Glu Val Phe Asn Tyr Glu Glu
 65 70 75 80

Leu Leu Glu Phe Ala Glu Gly Asp Ile Ala Lys Val Phe Gly Pro Glu
 85 90 95

Phe Ala Val Ile Asp Lys Tyr Pro Arg Arg Val Arg Leu Pro Ala Arg
 100 105 110

Glu Tyr Leu Leu Val Thr Arg Val Thr Leu Met Asp Ala Glu Val Asn
 115 120 125

Asn Tyr Arg Val Gly Ala Arg Met Val Thr Glu Tyr Asp Leu Pro Val
 130 135 140

Asn Gly Glu Leu Ser Glu Gly Gly Asp Cys Pro Trp Ala Val Leu Val

145		150		155		160
Glu Ser Gly Gln Cys Asp Leu Met Leu Ile Ser Tyr Met Gly Ile Asp						
		165		170		175
Phe Gln Asn Gln Gly Asp Arg Val Tyr Arg Leu Leu Asn Thr Thr Leu						
		180		185		190
Thr Phe Tyr Gly Val Ala His Glu Gly Glu Thr Leu Glu Tyr Asp Ile						
		195		200		205
Arg Val Thr Gly Phe Ala Lys Arg Leu Asp Gly Gly Ile Ser Met Phe						
		210		215		220
Phe Phe Glu Tyr Asp Cys Tyr Val Asn Gly Arg Leu Leu Ile Glu Met						
225		230		235		240
Arg Asp Gly Cys Ala Gly Phe Phe Thr Asn Glu Glu Leu Asp Ala Gly						
		245		250		255
Lys Gly Val Val Phe Thr Arg Gly Asp Leu Ala Ala Arg Ala Lys Ile						
		260		265		270
Pro Lys Gln Asp Val Ser Pro Tyr Ala Val Ala Pro Cys Leu His Lys						
		275		280		285
Thr Lys Leu Asn Glu Lys Glu Met Gln Thr Leu Val Asp Lys Asp Trp						
		290		295		300
Ala Ser Val Phe Gly Ser Lys Asn Gly Met Pro Glu Ile Asn Tyr Lys						
305		310		315		320
Leu Cys Ala Arg Lys Met Leu Met Ile Asp Arg Val Thr Ser Ile Asp						
		325		330		335
His Lys Gly Gly Val Tyr Gly Leu Gly Gln Leu Val Gly Glu Lys Ile						
		340		345		350
Leu Glu Arg Asp His Trp Tyr Phe Pro Cys His Phe Val Lys Asp Gln						
		355		360		365
Val Met Ala Gly Ser Leu Val Ser Asp Gly Cys Ser Gln Met Leu Lys						
		370		375		380
Met Tyr Met Ile Trp Leu Gly Leu His Leu Thr Thr Gly Pro Phe Asp						
385		390		395		400
Phe Arg Pro Val Asn Gly His Pro Asn Lys Val Arg Cys Arg Gly Gln						

405	410	415
Ile Ser Pro His Lys Gly Lys Leu Val Tyr Val Met Glu Ile Lys Glu		
420	425	430
Met Gly Phe Asp Glu Asp Asn Asp Pro Tyr Ala Ile Ala Asp Val Asn		
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Ile Ile Asp Val Asp Phe Glu Lys Gly Gln Asp Phe Ser Leu Asp Arg		
450	455	460
Ile Ser Asp Tyr Gly Lys Gly Asp Leu Asn Lys Lys Ile Val Val Asp		
465	470	475
Phe Lys Gly Ile Ala Leu Lys Met Gln Lys Arg Ser Thr Asn Lys Asn		
485	490	495
Pro Ser Lys Val Gln Pro Val Phe Ala Asn Gly Ala Ala Thr Val Gly		
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Pro Glu Ala Ser Lys Ala Ser Ser Gly Ala Ser Ala Ser Ala Ser Ala		
515	520	525
Ala Pro Ala Lys Pro Ala Phe Ser Ala Asp Val Leu Ala Pro Lys Pro		
530	535	540
Val Ala Leu Pro Glu His Ile Leu Lys Gly Asp Ala Leu Ala Pro Lys		
545	550	555
Glu Met Ser Trp His Pro Met Ala Arg Ile Pro Gly Asn Pro Thr Pro		
565	570	575
Ser Phe Ala Pro Ser Ala Tyr Lys Pro Arg Asn Ile Ala Phe Thr Pro		
580	585	590
Phe Pro Gly Asn Pro Asn Asp Asn Asp His Thr Pro Gly Lys Met Pro		
595	600	605
Leu Thr Trp Phe Asn Met Ala Glu Phe Met Ala Gly Lys Val Ser Met		
610	615	620
Cys Leu Gly Pro Glu Phe Ala Lys Phe Asp Asp Ser Asn Thr Ser Arg		
625	630	635
Ser Pro Ala Trp Asp Leu Ala Leu Val Thr Arg Ala Val Ser Val Ser		
645	650	655
Asp Leu Lys His Val Asn Tyr Arg Asn Ile Asp Leu Asp Pro Ser Lys		

660	665	670
Gly Thr Met Val Gly Glu Phe Asp Cys Pro Ala Asp Ala Trp Phe Tyr		
675	680	685
Lys Gly Ala Cys Asn Asp Ala His Met Pro Tyr Ser Ile Leu Met Glu		
690	695	700
Ile Ala Leu Gln Thr Ser Gly Val Leu Thr Ser Val Leu Lys Ala Pro		
705	710	715
Leu Thr Met Glu Lys Asp Asp Ile Leu Phe Arg Asn Leu Asp Ala Asn		
725	730	735
Ala Glu Phe Val Arg Ala Asp Leu Asp Tyr Arg Gly Lys Thr Ile Arg		
740	745	750
Asn Val Thr Lys Cys Thr Gly Tyr Ser Met Leu Gly Glu Met Gly Val		
755	760	765
His Arg Phe Thr Phe Glu Leu Tyr Val Asp Asp Val Leu Phe Tyr Lys		
770	775	780
Gly Ser Thr Ser Phe Gly Trp Phe Val Pro Glu Val Phe Ala Ala Gln		
785	790	795
Ala Gly Leu Asp Asn Gly Arg Lys Ser Glu Pro Trp Phe Ile Glu Asn		
805	810	815
Lys Val Pro Ala Ser Gln Val Ser Ser Phe Asp Val Arg Pro Asn Gly		
820	825	830
Ser Gly Arg Thr Ala Ile Phe Ala Asn Ala Pro Ser Gly Ala Gln Leu		
835	840	845
Asn Arg Arg Thr Asp Gln Gly Gln Tyr Leu Asp Ala Val Asp Ile Val		
850	855	860
Ser Gly Ser Gly Lys Lys Ser Leu Gly Tyr Ala His Gly Ser Lys Thr		
865	870	875
Val Asn Pro Asn Asp Trp Phe Phe Ser Cys His Phe Trp Phe Asp Ser		
885	890	895
Val Met Pro Gly Ser Leu Gly Val Glu Ser Met Phe Gln Leu Val Glu		
900	905	910
Ala Ile Ala Ala His Glu Asp Leu Ala Gly Lys Ala Arg His Cys Gln		

915	920	925
Pro His Leu Cys Ala Arg	Pro Arg Ala Arg Ser Ser Trp Lys Tyr Arg	
930	935	940
Gly Gln Leu Thr Pro Lys Ser Lys Lys Met Asp Ser Glu Val His Ile		
945	950	955 960
Val Ser Val Asp Ala His Asp Gly Val Val Asp Leu Val Ala Asp Gly		
	965	970 975
Phe Leu Trp Ala Asp Ser Leu Arg Val Tyr Ser Val Ser Asn Ile Arg		
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Val Arg Ile Ala Ser Gly Glu Ala Pro Ala Ala Ala Ser Ser Ala Ala		
	995	1000 1005
Ser Val Gly Ser Ser Ala Ser Ser Val Glu Arg Thr Arg Ser Ser Pro		
	1010	1015 1020
Ala Val Ala Ser Gly Pro Ala Gln Thr Ile Asp Leu Lys Gln Leu Lys		
	1025	1030 1035 1040
Thr Glu Leu Leu Glu Leu Asp Ala Pro Leu Tyr Leu Ser Gln Asp Pro		
	1045	1050 1055
Thr Ser Gly Gln Leu Lys Lys His Thr Asp Val Ala Ser Gly Gln Ala		
	1060	1065 1070
Thr Ile Val Gln Pro Cys Thr Leu Gly Asp Leu Gly Asp Arg Ser Phe		
	1075	1080 1085
Met Glu Thr Tyr Gly Val Val Ala Pro Leu Tyr Thr Gly Ala Met Ala		
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Lys Gly Ile Ala Ser Ala Asp Leu Val Ile Ala Ala Gly Lys Arg Lys		
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Ile Leu Gly Ser Phe Gly Ala Gly Gly Leu Pro Met His His Val Arg		
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Ala Ala Leu Glu Lys Ile Gln Ala Ala Leu Pro Gln Gly Pro Tyr Ala		
	1140	1145 1150
Val Asn Leu Ile His Ser Pro Phe Asp Ser Asn Leu Glu Lys Gly Asn		
	1155	1160 1165
Val Asp Leu Phe Leu Glu Lys Gly Val Thr Val Val Glu Ala Ser Ala		

1170	1175	1180
Phe Met Thr Leu Thr Pro Gln Val Val Arg Tyr Arg Ala Ala Gly Leu		
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Ser Arg Asn Ala Asp Gly Ser Val Asn Ile Arg Asn Arg Ile Ile Gly		
1205	1210	1215
Lys Val Ser Arg Thr Glu Leu Ala Glu Met Phe Ile Arg Pro Ala Pro		
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Glu His Leu Leu Glu Lys Leu Ile Ala Ser Gly Glu Ile Thr Gln Glu		
1235	1240	1245
Gln Ala Glu Leu Ala Arg Arg Val Pro Val Ala Asp Asp Ile Ala Val		
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Glu Ala Asp Ser Gly Gly His Thr Asp Asn Arg Pro Ile His Val Ile		
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Leu Pro Leu Ile Ile Asn Leu Arg Asn Arg Leu His Arg Glu Cys Gly		
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Tyr Pro Ala His Leu Arg Val Arg Val Gly Ala Gly Gly Gly Val Gly		
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Cys Pro Gln Ala Ala Ala Ala Ala Leu Thr Met Gly Ala Ala Phe Ile		
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Phe Cys Lys Tyr Asp Ser Phe Asp Ser Met Pro Pro Ala Glu Leu Glu		
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Arg Ile Glu Lys Arg Ile Phe Lys Arg Ala Leu Gln Glu Val Trp Glu		
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Glu Thr Lys Asp Phe Tyr Ile Asn Gly Leu Lys Asn Pro Glu Lys Ile		

1425	1430	1435	1440
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Arg Val Met Asp Tyr Gln Val Trp Cys Gly Pro Ala Ile Gly Ala Phe			
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<212> DNA

<213> Schizochytrium aggregatum

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<210> 75

<211> 30

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<213> Schizochytrium aggregatum

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30

<210> 76

<211> 4767

<212> DNA

<213> Schizochytrium aggregatum

<400> 76

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<210> 77

<211> 7959

<212> DNA

<213> *Vibrio marinus*

<400> 77

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<212> DNA

<213> *Vibrio marinus*

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<211> 6057

<212> DNA

<213> *Vibrio marinus*

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<211> 2910

<212> DNA

<213> *Shewanella putrefaciens*

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/52, 15/82, 5/10, 1/21, C12P 7/64, C11C 1/00, C07K 14/405, 14/28, A01H 5/00	A3	(11) International Publication Number: WO 00/42195 (43) International Publication Date: 20 July 2000 (20.07.00)
(21) International Application Number: PCT/US00/00956 (22) International Filing Date: 14 January 2000 (14.01.00) (30) Priority Data: 09/231,899 14 January 1999 (14.01.99) US (71) Applicant: CALGENE, LLC [US/US]; 1920 Fifth Street, Davis, CA 95616 (US). (72) Inventors: FACCIOOTTI, Daniel; 2636 Lafayette Drive, Davis, CA 95616 (US). METZ, James, George; 2830 Belhaven Place, Davis, CA 95616 (US). LASSNER, Michael; 721 Falcon Avenue, Davis, CA 95616 (US). (74) Agent: RAE-VENTER, Barbara; Rae-Venter Law Group, P.C., P.O. Box 60039, Palo Alto, CA 94306 (US).		(81) Designated States: BR, CA, IL, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> (88) Date of publication of the international search report: 28 September 2000 (28.09.00)
(54) Title: SCHIZOCHYTRIUM PKS GENES (57) Abstract The present invention relates to compositions and methods for preparing poly-unsaturated long chain fatty acids in plants, plant parts and plant cells, such as leaves, roots, fruits and seeds. Nucleic acid sequences and constructs encoding PKS-like genes required for the poly-unsaturated long chain fatty acid production, including the genes responsible for eicosapentenoic acid production of <i>Shewanella putrefaciens</i> and novel genes associated with the production of docosahexenoic acid in <i>Vibrio marinus</i> are used to generate transgenic plants, plant parts and cells which contain and express one or more transgenes encoding one or more of the PKS-like genes associated with such long chain poly-unsaturated fatty acid production. Expression of the PKS-like genes in the plant system permits the large scale production of poly-unsaturated long chain fatty acids such as eicosapentenoic acid and docosahexenoic acid for modification of the fatty acid profile of plants, plant parts and tissues. Manipulation of the fatty acid profiles allows for the production of commercial quantities of novel plant oils and products.		

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/52 C12N15/82 C12N5/10 C12N1/21 C12P7/64 C11C1/00 C07K14/405 C07K14/28 A01H5/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C12P A01H C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 55625 A (CALGENE LLC) 10 December 1998 (1998-12-10) the whole document	1-3, 5, 7, 17, 18, 20-25, 30-36, 38-40
A	EP 0 823 475 A (NAGASE SEIKAGAKU KOGYO KK ;SUNTORY LTD (JP); JAPAN AS REPRESENTED) 11 February 1998 (1998-02-11) the whole document	4, 6, 8-16, 19, 26-29, 37
A	WO 98 46764 A (THURMOND JENNIFER ;CALGENE LLC (US); ABBOTT LAB (US); KNUTZON DEBO) 22 October 1998 (1998-10-22) see esp. example 20; SEQ ID NO:47-50 --- -/--	4, 6, 8-16, 19, 26-29, 37
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> Patent family members are listed in annex.		
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Date of the actual completion of the international search 14 June 2000		Date of mailing of the international search report 06/07/2000
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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